HANDBOOK OF PHYSIOLOGY

SECTION 1: Neurophysiology, VOLUME III

# HANDBOOK OF PHYSIOLOGY

*Section 1: NEUROPHYSIOLOGY*

VOLUME I

Historical development of neurophysiology
Neuron physiology
Brain potentials and rhythms
Sensory mechanisms
Vision

VOLUME II

Motor mechanisms
Central regulatory mechanisms

VOLUME III

Neurophysiological basis of the higher functions of the nervous system
Central nervous system circulation, fluids and barriers
Neural metabolism and function
Neurophysiology: an integration

# HANDBOOK OF PHYSIOLOGY

*A critical, comprehensive presentation*

*of physiological knowledge and concepts*

---

SECTION 1:

# Neurophysiology

VOLUME III

*Editor-in-Chief:* JOHN FIELD

*Section Editor:* H. W. MAGOUN

*Executive Editor:* VICTOR E. HALL

*American Physiological Society*, WASHINGTON, D. C., 1960

Library of Congress Catalog Card No. 59-12957

Printed in the United States of America by Waverly Press, Inc., Baltimore 2, Maryland

Distributed by Williams & Wilkins Co., Baltimore 2, Maryland

# Contents

# Neurophysiological basis of the higher functions of the nervous system—introduction

WILDER PENFIELD *Montreal Neurological Institute, Montreal, Quebec*

CHAPTER CONTENTS



NEUROPHYSIOLOGISTS endowed with widely varied skills have joined together in the common enterprise of composing this book. Their contributions have advanced along a rising scale from neuron and brain potential to sensory mechanisms, motor mechanisms and transactional mechanisms. Thus the patient reader hears a swelling chorus of some 60 voices. Now that we have come to the neurophysiological basis of higher function we must turn our attention to man himself and to the mind of man. Here there is no full-toned harmony and the physiological voices are few and faltering.

## THE MOUNTAIN TOP

Those who hope to solve the problem of the neurophysiology of the mind are like men at the foot of a mountain. They stand in the clearings they have made on the foothills, looking up at the mountain they hope to scale. But the pinnacle is hidden in eternal clouds and many believe it can never be conquered. Surely if the day does dawn when man has reached complete understanding of his own brain and mind, it may be his greatest conquest, his final achievement.

In the meantime, what are scientists to say of the things unseen, the problems yet to be solved? Are they entitled to a special privilege as prophets? What should they say in advance about the nature of the mind, the existence of the spirit? What about monism, dualism, God?

In his Rede Lecture at Cambridge in 1933, Sir Charles Sherrington said: "I reflect with apprehension that a great subject can revenge itself shrewdly for being too hastily touched. To the question of the relation between brain and mind the answer given by a physiologist 60 years ago was 'Ignorabimus.' . . . The problem today has one virtue at least, it will long offer to those who pursue it the comfort that to journey is better than to arrive; but that comfort assumes arrival. Some of us—perhaps because we are too old—or is it, too young—think there may be arrival at last."

There is only one method that a scientist may use in his scientific work. This is the method of observation of the phenomena of nature followed by comparative analysis and supplemented by experimentation in the light of reasoned hypothesis. Neurophysiologists who follow the rules of the scientific method in all honesty will hardly pretend that their own scientific work entitles them to answer these questions.

Ivan Pavlov described the learning process, elaborating the mechanisms of conditioned reflexes. Sherrington explored the basic mechanisms of subconscious reflex action. Both were good scientists, and neither claimed that he had solved ultimate truths outside the confines of an animal laboratory.

Those who assert today that the work of Pavlov proved the truth of materialism draw a premature

conclusion. Those who hail Pavlov as the great monist and set Sherrington up against him as the leader of dualism go far beyond the evidence.

Sherrington in his laboratory was a cautious scientist who worked without preconceived prejudice. His pupils hardly suspected that outside the laboratory he was a poet and a philosopher. His book of poems was published when he was 68 years of age, and his philosophical monograph, *Man on His Nature*, when he was 80! At the age of 90, when he wrote the introduction to a new edition of his scientific magnum opus, he ventured no farther than to say: "That our being should consist of two separate elements, offers, I suppose, no greater inherent improbability than that it should rest on one only."[1]

Although in the laboratory he adhered to critical objectivity, he had faith that "the relation between brain and mind" would be solved—the mountain would be scaled in some distant day. Until then, he pointed out, neurophysiologists must carry on using the "language of separation" without prejudice as to what the final truth may prove to be. To speak of mind and brain is to employ the language of the common man, the language of dualism. But we can do nothing else if we would get on with the job.

Outside the laboratory, few scientists are to be considered poets or philosophers. But, nevertheless, most reasonable men must wonder about those mysteries which are not to be solved by the scientific method in their lifetime; such mysteries as: what lies beyond the grave? what is the origin of life, the design of the universe, the nature of truth?

Scientists are men as well as workers. They enter and leave life like other men. "There is a season and a time to every purpose under the heaven," and all must play, in turn, the role of child, husband, father and elder. Good scientists may well conclude that there is virtue in the concepts of life that have been passed along from father to son within the memory of man. Christian, Jew, Moslem and Hindu may have an intelligent faith in God and still be completely objective in scientific thought. The atheist can do the same, if he is also a good scientist.

Thus each man should turn to his workshop in his own 'clearing' without prejudice, and without lingering too long on the street corner to debate with Berkleian philosopher, or materialist or dualist. And I hasten now to return to my problem of writing an introduction to the chapters of this section on "The Neurophysiology of Higher Function."

[1] From the Introduction to the second edition of *The Integrative Action of the Nervous System*. London Cambridge, 1947.

## HIGHER FUNCTIONS

Man is said, by man, to be higher in the evolutionary scale than all other creatures. But how are we to define 'higher' as applied to the neurophysiology of the nervous system? Let us say that the neuronal mechanisms that are essential to consciousness are high, higher than certain reflex mechanisms. It is clear that in the central nervous system there are many involuntary mechanisms that have little or nothing to do with conscious states. The manifold activities of the decerebrate animal bear witness to this. Above this there is the neuronal activity associated with 'consciousness' and with the preparation for voluntary action, an activity that is essential to the very existence of these things.

Voluntary activity is produced by a flow of potentials along a well-known pathway from cerebral cortex to muscle. And the paths of sensory inflow that carry related information inward are well known as far as the cerebral cortex. But the cortex is not the end of the sensory pathway nor is it the beginning of the motor pathway.

It is the organizing and integrating activity that comes between this sensory input and this motor output that constitutes the physiological basis of the mind. Here is the 'higher function.' Here, the highest levels of integration are to be sought.

Physiologists have contributed little at this level, although the work of Magoun on the reticular activating system, and such contributions as those in the preceding chapters by Bremer, Brookhart, French, Jasper, Pribram, Kaada, Green, Pampiglioni and Gloor constitute a promising beginning.

However brief it may be, each stage must have a sequential time value. There is a time allowance for *a*) afferent conduction, *b*) centrencephalic organization, *c*) volitional efferent conduction and *d*) motor contraction. A man's awareness of environment during any moment of time cannot be present during the afferent conduction of that moment. It must follow. It must precede the outgoing volitional conduction, if appropriate action is taken.

This sequence must hold although preparation and overlap are, no doubt, important in such processes. To borrow from the thinking of William James, consciousness is continuous during our waking hours, but its content is never the same. Like a mountain brook it tumbles past in its rocky bed but the water cannot return nor be held in its place. From the standpoint of the physiologist too, the electrical potentials pass in swift and everchanging variation through the higher circuits of organization.

It might be considered hypothetically that that mechanism is highest which is functionally the closest to the zone of departure of the stream of potentials which, flowing outward, determines voluntary action. In the ganglionic zone of departure the pattern of the plan must become the pattern of the emerging motor stream. On arrival at the muscles, the pattern of that stream is translated into act or word.

Abstract thinking, which has no outward expression, differs no doubt from that which produces continuous voluntary action such as talking, or writing or playing football, and yet many of the functional units of integration must be the same.

## CLINICAL SURMISES

There are many inferences that come to a clinician. Perhaps it may serve a useful purpose to set down a few observations and thoughts which seem to shadow forth the outlines of functional organization in the human brain. Substantiation of most of these statements may be found in previous publications elsewhere.

Many patients have been operated upon under local anesthesia to cure them of recurring attacks of focal epilepsy. In the course of such operations, nearly all areas of the cerebral cortex have been excised at one time or another, all except the most precious, the major speech areas of the dominant hemisphere. Furthermore, all areas, including those devoted to speech, have been stimulated repeatedly—since this is one way of discovering the abnormal zone which must be excised if the sufferer is to be relieved of his fits.

These subjects, who help the surgeon with so much steadfast courage, have reported to him movements, sensations and certain psychical phenomena that are produced by application of a gentle electric current to the cortex. These constitute[2] data that no laboratory 'preparation' can provide.

Electrical stimulation of the cerebral cortex of a fully conscious man produces positive 'physiological' responses, but only in certain areas. These excitable areas yield, when conditions are favorable and the stimulating current is at a threshold level, three principal types of physiological responses: *a*) motor, *b*) sensory and *c*) psychical.

[2] Over the years, these data have been recorded carefully in the Montreal Neurological Institute with the invaluable assistance of Herbert Jasper, Theodore Rasmussen, Theodore Erickson, Edwin Boldrey, Lamar Roberts, Anne Dawson and a succession of brilliant assistants.

## SENSORY AND MOTOR RESPONSES

There are 'sensory' and 'motor' areas that may be considered secondary or supplementary. These areas yield responses, when stimulated, that seem to the patient just as compelling as those obtained from the better known primary areas. But I shall refer here only to the latter: the excitable motor strip on the Rolandic or precentral gyrus, the somatic sensory area on the postcentral gyrus, the visual sensory area in the calcarine fissure and the auditory sensory area that carpets Heschl's transverse gyrus deep in the fissure of Sylvius.

One conclusion is clear: these sensory areas, that occupy homologous positions in each hemisphere, are way stations in the afferent streams of impulses that lead from the periphery to some deep subcortical target. The precentral gyrus, on the other hand, is a way station in the efferent pathway that arises in subcortical gray matter and passes outward to the muscles of voluntary action.

Circumexcision of cortical areas, sparing these sensory or the motor areas, does not stop functional conduction through these way stations. For example, when the parietal cortex of the right hemisphere is excised the subject is still able to guide the left hand in voluntary movement according to the information received from the left visual field that entered the brain through the right visual cortical area. The guidance is obviously not provided by direct cortical interconnection.

It seems fair to conclude that corticocortical 'association' connections between one functional area of cortex and another are of comparatively minor importance. This contradicts a long-cherished hypothesis that the cortex was somehow invested with miraculous mechanisms of integration.

Electrical stimulation of the cortex, which produces sensory or motor responses, does so by producing neuronal conduction in the direction of the normal flow through the particular way station to which the electrode is applied. This neuronal conduction may therefore be considered dromic, and the effect is produced by activation of nerve cell stations farther along in the stream of normal flow.

The electrode applied to the precentral gyrus thus produces simple movement of the opposite fingers by conduction to the anterior horn cell clusters in the cervical spinal cord; or, if applied elsewhere, it produces vocalization, by conduction to the vocalization and respiratory mechanisms in the lower brain stem.

Thus, the electrode provides no direct information as to what functional contribution the cortex may

make at these junction points. It does prove something about the dromic connections of each area.

The electrode, applied to a sensory area, produces seeing or hearing or feeling, depending upon which area is stimulated. The sensation, if somatic, is tingling, numbness or a sense of movement in some part; if visual, it is moving lights or colors or stars; if auditory, it is a buzzing, ringing, whispering or thumping sound. These are the elements of the sensory input.[3]

The exploratory electrode, delivering, for example, 60 pulses per sec. lasting 2 msec. with an intensity of 3 v., produces these three different categories of sensation because the cortical areas are connected with three different receiving stations in the higher brain stem. That same electrode, when it applies the same current to the precentral gyrus, produces movement because of the corticofugal connections with motor mechanisms in the cord or lower brain stem.

However, under normal functional conditions, the flow of impulses that activates the precentral gyrus for voluntary movement must arise in subcortical gray matter since excision of cortex in front of the gyrus or behind it does not prevent a man from carrying out voluntary action based on sensory information.[4]

## CENTRENCEPHALIC ORGANIZATION

Therefore, the hypothesis presents itself that much of the organizing neuronal activity between sensory input and motor output must depend upon circuits and ganglionic structures within the higher brain stem, if the brain stem as defined by Herrick is understood to include the thalamic nuclei of the two hemispheres. This old central structure, including the diencephalon, mesencephalon and at least part of the metencephalon, is connected by symmetrical projection tracts to the various functional areas of the cerebral cortex on either side.

Thus by means of these connections each area of cortex could, it seems, be employed in common integrated action. There is no other obvious set of essential interconnections for one cortex with the other cortex and one cortical area with its neighboring cortical areas. Direct transcortical connections can be interrupted with relative impunity. Even complete section of the corpus callosum by a number of intrepid neurosurgeons has had astonishingly little effect on the intellectual activity of man.

One-sided removal of, or injury to, any area of cerebral cortex does not abolish conscious thinking. It may change the content of awareness, interfere with voluntary acts, render less effective planned action, deprive the patient of word symbols—but he still thinks and weeps, perhaps, at his own pitiful incapacity.

On the other hand, interference with the centrencephalic system of the higher brain stem produces loss of consciousness. In the presence of deep coma due to a small critically placed local lesion in the higher brain stem, the motor mechanisms may seem to remain intact. The patient lies in bed and moves occasionally as in deep sleep, like the enchanted 'sleeping beauty' of the French nursery tale.

It is accepted by those familiar with epilepsy that epileptic discharge originates in gray matter, never in white matter. When epileptic discharge occurs in the gray matter of the centrencephalic system of the higher brain stem, the patient is initially unconscious because the discharge interferes with local ganglionic function. On the other hand, a partial seizure, due to restricted epileptic discharge in any area of gray matter of the cerebral cortex, is not associated with initial unconsciousness.

The system of nerve fibers and ganglionic centers within the brain stem may be called centrencephalic since, because of its central position, it provides symmetrical connections with the whole brain. Through it, one may suppose that this part of the cortex, or that part, could be used simultaneously or in sequence, depending upon the pattern and the requirements of the existing state of consciousness.

## FLASH-BACK MEMORY AND COMPARATIVE INTERPRETATION

From the temporal cortex of either side, electrical stimulation or local epileptic discharge may produce phenomena of an entirely different order from the motor and sensory responses previously produced in animals and man. These responses are 'psychical,' to borrow an adjective from Hughlings Jackson. He described such phenomena as they were experienced by his epileptic patients during small fits. "Dreamy states," he called them, "as if I went back to all that occurred in my childhood."

[3] In Chapter LX, William Neff points out also that the "input of the sensory systems may be controlled at a number of levels . . . through centrifugal pathways."

[4] In Chapter LXVII, Jacques Paillard has summarized the evidence in favor of "a subcortical origin of the voluntary commands." His study of the patterning of skilled movements is as clear as it is stimulating.

Psychical responses may be produced occasionally in conscious man by gentle stimulation of the cortex of the temporal lobe. The response is ordinarily physiological and does not outlast the application of the electrode to the gray matter. The responses are of two types: illusion of comparative interpretation of the present, and hallucination of re-enactment of previous experience.

Thus, the first type of response, if interpretive, gives the patient a sudden sense of alteration in the meaning of things being seen or heard or experienced at the moment. He finds them suddenly familiar, or strange, or more distant, nearer, fearful, etc. In normal life we assume that such feelings must result from comparison of the present experience with similar past experiences, although this comparison of present with past is carried out subconsciously.

If the response to stimulation is hallucinatory, it proves to be a re-enactment, or 'flash back,' of previous experience. The patient is aware of all those things to which he paid attention in some previous period of time. The experience unfolds for him at the former rate of speed as long as the electrode is held in place. He is aware of the present and of the past as well. If he hears music, it is a specific rendition as he heard it years ago, perhaps. He may see the orchestra or the piano or the singer, and he may feel again the emotion roused in him by the music during that distant strip of time.

Thus it is clear that the temporal cortex has some sort of selective connection with a detailed flash-back record of the past, most of which has been forgotten as far as the individual's ability for voluntary recall is concerned.

## HIGHER FUNCTIONAL MECHANISMS

It would seem that, under normal circumstances, this flash-back record is reopened when similar experience presents itself. For example, the reappearance of a long-forgotten friend makes available his previous records so that he seems familiar at once, and minor changes in him are obvious. Take another example: the set of present circumstances is compared with similar experiences from the past which may have been dangerous or painful and the subject feels a fear that calls for action.

By inference, therefore, one may surmise that the temporal cortex normally plays some role in a subconscious scanning mechanism that opens the flash-back memory file and provides a signal of comparative interpretation (familiar, fearful, etc.) which rises without warning into consciousness.

This scanning of the flash-back memory forms one partially separable mechanism in the higher functions of the brain. The use of words in symbolic thinking, so well described in Chapter LXVIII by Zangwill, is another such mechanism. Some degree of localization of the cortical portion of these mechanisms is possible now, but not the centrencephalic portions. Nevertheless this is a beginning of the delineation of functional units closely related to conscious thinking.

Hughlings Jackson pointed out that there were levels of integration in the nervous system and attempted to assign an ascending 'representation' and 're-representation' to spinal cord, cerebral cortex and frontal lobes. But it is clear now that, although there are advancing stages in the progressive organization that make conscious thinking possible, these stages cannot be assigned to separable major areas of the brain.

A neurophysiologist might well attempt to separate the levels of organization involved in normal voluntary activity on the basis of the progressive lapse of time, the period of afferent conduction, the period of organization and integration, the period of efferent conduction. From a functional point of view the mechanisms of that middle period of time are the highest and seem the most complicated. They form the physical basis of the mind. Doubtless, many of the mechanisms that are usable in this middle period are also variously employed during aimless conscious states and in constructive abstract thinking.

The neuron circuits of these functional mechanisms are to be found in the higher brain stem and in the cerebral cortex, joined together in action patterns that form themselves and vanish and form anew, making combinations never twice the same. Generations of workers must employ the scientific method to study man in health and in disease.

Thus the shadowy outlines we perceive today will take clear form in a neurophysiology of higher functions. And if man comes to understand himself in mind and body he will have made his greatest conquest. Perhaps then he will recall the prediction that "the truth shall make you free."

# Sensory discrimination

WILLIAM D. NEFF *Laboratory of Physiological Psychology,*[1] *University of Chicago, Chicago, Illinois*

CHAPTER CONTENTS



IN OTHER CHAPTERS, the function of each of the sensory systems has been discussed in detail. It is the purpose of this chapter to consider the information we have for all the senses in a less specific fashion and to look for common principles which may have emerged in the search for neurophysiological explanations of sensory discrimination.

To the sensory physiologist or psychologist, the meaning of the phrase 'sensory discrimination' needs no explanation. To others, its meaning may not be clear immediately. Therefore, a brief explanation is in order. The living organism makes a sensory discrimination when it shows by its behavior that it has made a response to a change in a physical stimulus applied to one of its sense organs. It may respond to the presence or absence of a particular stimulus or may make a choice between two or more stimuli. When man is used as a subject in an experiment on sensory discrimination, he may be instructed to report verbally when a stimulus change occurs; often he is asked to respond by pushing a button or by making some other nonverbal response. When a lower animal is used as an experimental subject, it is usually trained to indicate the stimulus change by making a movement, such as flexing a leg, pressing a lever with its foot or moving from one position to another in the test apparatus. In each case, the discrimination consists simply of a motor response to a change in some aspect of a physical stimulus which acts upon the sensory end organs.

## HISTORICAL SUMMARY[2]

The nature of the questions asked and of the approaches taken in current research on sensory discrimination can best be understood after a brief consideration of the history of scientific investigation of the sensory systems.

### *The Beginning of Scientific Inquiry*

There is no evidence to indicate that learned men of pre-Hellenic times attempted to account for how man perceives the world by making careful observations and logical speculations; they were inclined to account for natural phenomena in terms of the superstitions and religious dogmas of their particular civilizations.

Greek scholars did observe carefully and speculated wisely. Handicapped by lack of knowledge—

[1] The Laboratory of Physiological Psychology is supported by the Office of Naval Research and the Air Force Office of Scientific Research.

[2] This historical summary is based for the most part on secondary sources. For more complete accounts of the history of the neurophysiology of sensation, the reader is referred to the works of Boring and others (26, 28, 30, 46, 50, 63, 64).

limited and inaccurate notions about the physical environment, incomplete information about gross anatomical structures, almost no evidence, and mistaken ideas about the relation of sense organs to the brain or other parts of the body—they nevertheless proposed theories of perception which, although wrong, were reasonable.

For example, Empedocles (*ca.* 490–430 B.C.) introduced a theory of sensation which can be stated approximately in these words. The organ of vision contains a lantern and the organ of hearing, a bell or gong. The lantern in the eye is lighted and the gong in the ear rung by outer light and sound, respectively. The light in the eye and the ringing in the ear are then conveyed in some fashion to the 'point of sense' and thus the light and sound are perceived.

Theophrastus (*ca.* 372–287 B.C.) criticized Empedocles' theory of hearing as follows: "Empedocles explains hearing by stating that it is due to intra-aural sounds. But it is strange of him to suppose that he has made it self-evident how we hear by merely stating this theory of a sound, as of a gong, within the ear. For suppose that we hear the outer sounds by means of this gong; by what do we hear the gong itself when it rings?"[3]

Translating this argument into modern terms, we might think of Empedocles as representing those investigators and theorists who have emphasized peripheral analysis and who have proposed so-called 'theories' of sensation which are actually theories of end organ function. And Theophrastus stated quite aptly, almost 2500 years ago, the criticism which has sometimes been made in recent years, namely that having accounted for how light, sound, odors or other sensory stimuli are received and analyzed by the sense organs, there still remains the formidable task of discovering how this information is coded and transmitted into the central nervous system and how it is utilized there to bring about discriminatory responses.

Not only Empedocles and Theophrastus but many others of the Greek philosophers contributed to the discussion and theorizing on the problems of sensory perception. Aristotle, for example, classified the senses into five groups: vision, hearing, touch, taste and smell, a classification scheme that was to remain acceptable to most scholars until a sixth, the muscle sense, was recognized and added at the start of the nineteenth century.

Despite this early show of interest, some 2000 years elapsed with little further advance in knowledge of sensory mechanisms. There were, of course, important discoveries in the fields of physics and anatomy, discoveries which prepared the way for later scientific investigations. The physics of light and sound were at least partially understood and, equally important for later psychological and physiological investigations, instruments were developed for controlling production of sound and light. In anatomy, it became an acceptable practice (in some places and in some times) to dissect animals or human cadavers, and the development of the compound microscope and of techniques for preparing tissues for microscopic examination led to the discovery of many details of the structures of the end organs and of their connections with the central nervous system.

The philosophers of the seventeenth and eighteenth centuries also made a contribution by emphasizing the importance of the senses as the essential channels by which the living organism is able to have an awareness of the external environment.

The field was set then at the beginning of the nineteenth century for the launching of a scientific attack upon the problems of sensory discrimination or, as it might have been put by the scholars of that period, the problem of how man knows the external world. In a brief historical summary, it is impossible to give due credit to all who made contributions in any given field. As a mnemonic device, it is excusable, perhaps, to select the names of some men who have traditionally been accepted as leaders in doing research and in influencing the research and thinking of their colleagues and students.

### *The Modern Period*

It is fitting to begin a discussion of modern research in sensory discrimination with a reference to Johannes Müller and his doctrine of specific nerve energies. The doctrine or theory that Müller expounded, first in 1826 and in greater detail in 1838 and 1840, was not new with him. The same basic ideas can be traced back at least to John Hunter in 1786 and were expressed indirectly by Thomas Young in 1801 and quite explicitly by Charles Bell in 1811. It was, nevertheless, Müller who gave the 'theory' a name, even though a misleading one, and who formulated in detail 10 laws or propositions and

[3] The example of the contrasting viewpoints of Empedocles and Theophrastus is taken from Beare (17).

supported them by evidence based upon careful observations.

The main points of Müller's doctrine were the following.

*a*) Sensation is an awareness of the states of the sensory neural pathways and not of the environment directly. Müller gave strong emphasis to this part of his theory, stating it in slightly different forms in several of his 10 laws. He undoubtedly felt that this emphasis was necessary in order to refute the theory which had been accepted with little change by most scholars and scientists from the time of Empedocles, namely that an image of the stimulus entered the sense organ and in some manner was transmitted to the 'sensorium' or sensing center in the brain.

*b*) When a given sensory nerve is excited, the same kind of sensory experience results no matter what the nature of the stimulus. For example, when the optic nerve is excited by light waves striking the retinal receptors, by mechanical pressure (externally or internally produced) directly affecting the optic nerve or by electric shock applied to the nerve, the result is a visual sensation. For the auditory nerve, the result is always a sensation of sound, and so on for the other sensory modalities.

*c*) The same physical stimulus applied to different sense organs or sensory nerves gives rise to different sensations, in each case to the sensation appropriate to the organ or nerve in question. For example, electric shock applied to the optic nerve produces a visual sensation; to a tactual nerve, the sensation of touch.

Müller accepted the concepts of 'adequate stimulus' and 'specific irritability' of sense organs which had been expressed by other biologists before him. He gave a straightforward answer to the very important question: where does the 'specific energy' reside, is it a characteristic of the peripheral nerve or of centers in the central nervous system? His answer was that he did not know. He explicitly stated: "The peculiar mode of reaction of each sense, after the excitement of its nerve, may be due to either of two conditions. Either the nerves themselves may communicate impressions different in quality to the sensorium, which in every instance remains the same; or the vibrations of the nervous principle may in every nerve be the same and yet give rise to the perception of different sensations in the sensorium owing to the parts of the latter with which the nerves are connected having different properties" (50, p. 166).

The doctrine that activity in separate peripheral nerves or in their central connections forms the basis for different sensations was soon extended not only to account for vision, hearing, touch, smell and taste but for the sense qualities within each of these modalities.[4] As we have noted above, Thomas Young is often credited with having suggested a specific nerve energy theory a number of years before Müller's first publications on the subject. Young's suggestion was not made in an attempt to account for differences among the major senses but to account for the different colors perceived visually. He proposed the notion that there might be three kinds of receptors and connecting nerve fibers subserving the three primary colors.

Helmholtz made use of the principle of specific nerve energies to explain different qualities of sensation in both vision and hearing. He elaborated upon Young's earlier hypothesis and, giving due credit to Young, postulated specific nerve energies for the primary colors. The theory which he put forward is still referred to as the Young-Helmholtz theory of color vision.

In hearing, Helmholtz sought to explain pitch perception in terms of the specific nerve energy principle. The Helmholtz resonance theory of hearing stated that resonators in the cochlea analyze sounds so that sensory receptors and their connecting nerve fibers are selectively stimulated, and that each discriminable pitch is represented by a specific receptor or receptors and corresponding neural connections.

In the search for specific receptors for individual sense qualities, Blix in 1882 and Goldscheider in 1884 explored the surface of the skin for spots having specific sensitivity to the qualities pressure, warmth, cold and pain. They, and later von Frey, were able to identify spots for pressure, warmth and cold, with the question of spots for pain being a matter of some controversy. Von Frey also attempted to identify particular receptor endings in the skin for each of the separate qualities.

For the other senses, a direct attempt to identify separate receptors for different sensory qualities was less easy. That the sensory receptors for taste were associated with the papillae on the tongue had been

[4] Here and in the discussion which follows, modality is used in referring to one of the principal senses, namely to vision, hearing, somesthetic sense, kinesthetic sense, vestibular sense, taste or smell. The term 'attribute' will be used to refer to any discriminable dimension within a given sense, e.g. differences in intensity, in space, in duration or in quality. For a definition of 'sense quality,' see p. 1457.

deduced by Haller in 1763; Bell and Müller agreed with this opinion. Horn in 1825 showed experimentally that different regions of the tongue were more or less sensitive to various taste stimulating substances. The taste buds were identified and described by both Schwalbe and Lovén in 1867. But even after the specific nerve energy theory had been formally proclaimed, and thus the importance of isolating specific receptors emphasized, no evidence was forthcoming which would make possible the identification of structural differences among the receptors, differences which might be correlated with differences in function. Numerous investigators explored the tongue of human subjects, recorded the taste sensations reported in response to stimulation with different substances and prepared schemes for classifying the sensory qualities of taste.

The olfactory receptive area was described in 1882 by Schultze but, as with the taste buds, no evidence was obtained which suggested a relation between types of receptor and olfactory sensations. Many elaborate schemes of classifying discriminable odors were constructed on the basis of psychophysical experiments.

Charles Bell is sometimes given credit for discovering the muscle sense, but historians have pointed out that a number of other investigators had published papers suggesting a sixth sense before Bell's 1826 publication. They had been less successful in getting the idea of an additional sense adopted. Sensory receptors (muscle spindles) in muscle were first isolated by Kühne in 1863. Sherrington in 1894 showed that the muscle spindles were innervated by nerve fibers from the dorsal spinal roots and presumably had a sensory function.

Although the vestibular sense was not at the time considered to belong with the other primary senses, the presence of sense organs in the nonauditory labyrinth which were stimulated by position or movement of the head had been demonstrated by Fluorens in 1824. Since stimulation of the vestibular end organ does not give rise to specific, qualitatively distinct sensations in the same way that stimulation of other sensory organs does, no attempt was made to classify qualities of vestibular sensation. Nevertheless, Fluorens and later investigators did seek to discover separate functions for the major subdivisions of the vestibular end organ, namely the semicircular canals, the utricle and the saccule.

Coincident with the development of these new hypotheses as to the anatomical and physiological bases of sensory discrimination was another line of attack upon the problem of how the physical world is perceived by the living organism. E. H. Weber in 1834 began, and G. T. Fechner during the period 1851–1879 and W. Wundt from 1858 to 1920 extended a series of experimental investigations in which the aim was to establish systematic relationships between the physical attributes of external stimuli and the psychological attributes of sensation. Their work in this new field, later labeled psychophysics, established the foundation upon which was built a new branch of science, experimental psychology. Although the procedures which they and their followers used did not call for direct observation of physiological events, the theories of sensation to which the psychophysicists contributed have usually been expressed in terms of physiological events. In many instances, the results of psychophysical studies have set problems for physiological investigations. Psychophysics has also made important contributions to physiology of sensation by its development of methods of measurement, particularly methods of measuring absolute and differential thresholds, and by creating and assisting in satisfying a need for instruments which make possible the production and exact control of physical stimuli.

The last half of the nineteenth century was marked by a number of other developments which were important to the advance in scientific knowledge of sensory discrimination. Increased interest in the sense organs and the central nervous system led to their careful examination by microscopic techniques. The techniques, at first crude—the dissection and examination of fresh tissues under the microscope—were rapidly improved. Sense organs and neural tissues were treated with fixatives or hardening solutions, thus making dissection easier. A next and more important step forward was taken when analytical staining methods were discovered by Golgi in 1873 and Ehrlich in 1886. Their methods and those developed by others such as Ramón y Cajal, Nissl, Weigert and Marchi began to reveal for the first time details of the structures which mediate sensation.

The neural pathways were traced from sense organs into the central nervous system and, at least partly because of the influence of specific nerve energy theory, localization of separate regions subserving the different senses was sought in the highest centers, particularly in the cerebral cortex. The methods of architectonics were applied, and the cortex was subdivided into many regions of supposedly special function, the sensory projection

regions being prominent in most maps so produced.

In experiments on animals, regions of the cerebral cortex which were thought to be sensory projection areas were ablated and the effects on sensory discrimination were observed or tested crudely. In the clinic the effects of brain damage on sensory perception of patients were observed.

During the last part of the nineteenth century, considerable progress was also made in the use of electrical stimulating and recording techniques to explore the central nervous system. As Brazier (30) has pointed out, it was known by the end of the nineteenth century that changes in electrical activity can be recorded from the cerebral cortex in response to sensory stimulation. Better instrumentation was needed, however, before the full value of electrophysiological methods could be realized.

There have been a number of significant methodological advances which have marked the study of the senses during the twentieth century. First, and most important, has been the rapid development of new techniques in electrophysiology. Second has been the use of the behavioral testing methods of the comparative psychologist in studies of sensory function in animals. Third has been the refinement of techniques of experimental surgery. Fourth has been the improvement of instruments for production of sensory stimuli; in many instances, science has profited from the expansion of electronics in industry. Finally, a most important trend which can be seen today is the application of many techniques in a single experiment. Methods of electrophysiology, of neuroanatomy, of psychophysics and of psychophysiology are often used in a single investigation.

## NEUROPHYSIOLOGICAL BASIS OF SENSORY DISCRIMINATION

### *The Primary Sense Modalities*

In his doctrine of specific nerve energies, Johannes Müller offered an explanation, in anatomical and physiological terms, for discrimination of the primary sensory modalities: vision, hearing, touch, taste and smell. Others extended the theory to account for differences in sense qualities. In examining the present status of neurological theories of sensory discrimination, let us also start with the broader problem of how the sense modalities are differentiated and then go on to the more difficult task of evaluating the evidence for the neural mechanisms underlying discrimination of attributes of sensation.[4]

The specific nerve energy doctrine assumed that each primary sense modality had its separate nerve supply and separate representation in the central nervous system. An accumulation of evidence from experiments using a variety of anatomical and neurophysiological techniques has shown the essential correctness of this basic assumption. Thus, nerve fibers from the retina can be traced to the lateral geniculate bodies in the thalamus and thence to the striate cortex of the occipital lobes. In the auditory system, similarly, a direct restricted pathway can be traced from the cochlea to a limited region of the cortex of the temporal lobe via the primary cochlear nucleus, superior olivary complex, inferior colliculus and medial geniculate body. Receptors for the skin senses project to the parietal lobe, again having passed upwards through definite channels in the spinal cord and brain stem. Pathways for nerve fibers from taste and smell receptors have been carefully traced into the central nervous system, but here the evidence for final projection centers is not as clear as for the visual, hearing and somesthetic systems. Pathways for kinesthetic receptors are parallel and in close relation to those for the skin senses and apparently end in the same region of the cerebral cortex. Although it was at one time thought that the vestibular system differed from the other afferent systems in that it did not project to the cerebrum but had only reflex connections via lower brain-stem centers, evidence has been obtained in recent years which indicates an afferent pathway paralleling that of the auditory system and ending in an area of the temporal lobe which is usually considered to be part of the auditory projection region. On the afferent side, at least, the structural organization for discrimination based upon a place or topographical principle appears to be present in most mammalian species for all of the major senses.

First scientific evidence for topographical organization of the sensory systems came from clinical studies of the effects of brain lesions produced by disease, accident or surgery, and from experimental ablation studies in lower animals.[5] For the visual and tactual systems, in particular, it was clear that limited lesions of ascending pathways or of relatively small cortical areas result in sensory deficit. For the

[5] Brief historical summaries of this topic are available (14, 46, 63, 64, 66, 95, 137, 157, 189, 213).

other systems, the evidence was, and to some extent still is, controversial.

Studies of cortical cytoarchitecture and, more important, tracing of anatomical pathways by selective staining techniques provided further evidence of the basic structural organization of the sensory systems.[5] The most important advances, however, were made when electrophysiological methods were used to trace the sensory pathways in the central nervous system. The use of the evoked potential method has been of special value in mapping the areas of the cerebral cortex to which the primary sensory systems project. (See particularly Chapters XVII through XXI, XXIV and XXX of this *Handbook* for studies of individual projection areas.)

The increased knowledge gained through electrophysiology has not led to a sudden clarification of the significance of topographical organization. Rather, it has brought to light a complexity of organization, the significance of which remains to be explained. For example, at the cortical level, the primary projection areas as defined by cytoarchitecture, myeloarchitecture or tracing of degenerating pathways to or from thalamic nuclei were once thought to be unitary regions confined to relatively small portions of the main cerebral lobes. Evoked potential maps have shown that for the visual, somesthetic and auditory systems, at least, and for most mammals that have been studied, the regions of primary projection are more extensive than was formerly thought and they are not unitary, that is there may be two or more projection areas or two or more subdivisions of the projection region for each system. In all mammals (man included) that have been examined, two or more somatic areas have been found, evidence for duality of projection being that the different parts of the body project in an orderly fashion in two separate but adjacent areas. Likewise, in most mammals two visual areas and two auditory areas can be defined (see Chapters XXIV and XXX). Evidence for dual projection of visual and auditory systems in primates is not conclusive, but this lack of evidence may be due to difficulties encountered in exposing and in adequately exploring the relevant regions. The dual projection areas discovered by the evoked potential method in many instances have also been shown to be different with respect to their thalamic connections. For the visual, auditory and somatic systems there is some evidence that there may be three or more projection areas which must, in terms of internal organization, be considered as distinct.

The naming of multiple projection areas has not been simply the subdividing of the regions classified as projection cortex by the older anatomical methods; parts of the cortex formerly called 'association' areas have now been shown to have direct afferent connections with the thalamic nuclei of the main sensory systems. Consequently, the sensory projection areas, as now defined, occupy a larger portion of the total cortex than was once thought to be the case. In mammals below the primates, there are only small strips of 'silent' cortex lying between the visual, auditory and somatic projection regions. Even in primates, the extent of so-called association cortex is reduced in cortical maps based upon the latest electrophysiological studies.

While it was recognized that many reflex responses to sensory stimulation can be carried out via connections in the spinal cord or in brain-stem centers, it has been the common view, until relatively recent times, that conscious discriminations or learned discriminations depend upon the intactness of the appropriate regions of the cerebral cortex. Despite convincing evidence from experiments on lower animals and the lack of critical evidence from clinical investigations of man, this view is still expressed or implied by many writers of textbooks and even by some authors of current research publications.

Evidence bearing on the role of the cerebral cortex in sensory discrimination will be dealt with in more detail below when the neural mechanisms of different kinds of discrimination are discussed. In conjunction with the present discussion of the topographical organization of the primary sensory modalities, it is appropriate to note that, with the possible exception of vision in man, evidence from both clinical and experimental investigations indicates that for each of the sensory systems that has been studied carefully, some kinds of learned discrimination can be made after complete destruction of the cortical projection areas of that system.[6] In subprimate mammals, it has been shown that a learned discriminatory response to a sensory cue such as the flashing of a light, onset of a fairly loud tone or tactual stimulation of the skin can be established after complete or nearly complete ablation of all cerebral cortex (32, 75).

As we shall see, the capacity for sensory discrimination may be altered by more limited abla-

[6] It must be kept in mind, however, that we do not have clinical cases with lesions suitable for comparison with lower animals in which the sensory projection areas of a single system have been completely ablated bilaterally.

tions confined to cortical projection areas, but the ability to make certain discriminations remains.[7] The effects of interrupting sensory pathways at thalamic, tectal, bulbar or lower levels cannot be summed up so readily. Evidence to date is quite limited and will have to be considered in relation to particular kinds of discrimination.

*Discriminable Dimensions of Sensation*

A primary sensory modality may be defined as a sense organ or system of sense organs which has its adequate stimulus and which is connected to higher centers by its own separate nerve pathway.[8] Difficulty arises in deciding upon the total number of primary modalities. Vision, hearing, smell, taste, kinesthetic and vestibular systems can be differentiated readily. A question remains as to whether or not the somesthetic sense should be divided into a number of modalities, at least into three (touch, temperature and pain) and perhaps into more (light touch, deep pressure, warmth, cold and pain). This problem may be resolved when sufficient evidence is accumulated from experiments or, as seems more likely, it may cease to be considered an important problem.

For the purposes of the present chapter, we shall classify as separate sensory modalities the following: *a*) vision, *b*) hearing, *c*) somesthesis (touch, temperature and pain), *d*) kinesthesis, *e*) vestibular sense, *f*) taste and *g*) smell.

Discovering the neurophysiological basis for discrimination between primary sense modalities is only the beginning of an understanding of sensory discrimination. The next step is to look for mechanisms to account for discrimination within each sense since man and lower animals can make discriminations based upon differences in the characteristics of the stimuli affecting a single sensory modality.

On the basis of psychophysical experiments in which the essential method was that of controlled introspection, Wundt, Titchener and other psychologists of their time concluded that sensory experience can be described in terms of basic attributes such as intensity, quality, duration, extensity and clearness (attensity).[9] In the sections which follow, we have chosen to discuss the neurophysiology of sensory discrimination under headings, many of which are reminiscent of the categories set up by psychologists of the introspection school.

In attempting to bring together data from physiological, psychophysical and psychophysiological experiments, a complication arises which can lead to confusion unless it is recognized in advance and kept in mind during the subsequent discussion. In physiological experiments, parameters of the physical stimulus, such as intensity and frequency (or wave length), are varied and physiological changes, such as rate of impulses in a nerve fiber and number and position of fibers excited, are measured. In psychophysical experiments, the same physical parameters are varied and discriminations of the experimental subject recorded. The results of psychophysical studies have shown, however, that changes in a single dimension of discrimination are not necessarily a function of changes in a single dimension of the physical stimulus. Thus, brightness discrimination in vision is a function not only of light intensity but also of wavelength, and pitch discrimination in hearing is a function of both frequency and intensity of sound. The physiological events which are the basis of brightness or of pitch discrimination must then, in each case, be a function of at least two parameters of the respective physical stimulus.

In psychophysiological experiments, physiological events are varied and changes in sensory discrimination measured under different conditions of peripheral stimulation, the usual parameters of physical stimuli being varied, but in this case measurements are made of changes in discrimination before and after manipulation of a physiological condition. Difficulty arises when the results of physiological experiments, e.g. the variation in flow of nerve impulses with change in intensity of peripheral stimulation, are used in hypothesizing a neural mechanism to account for a change observed in a psychophysiological or psychophysical experiment. If, for example, pitch discrimination is a function of both intensity and frequency of sound, then the neural correlates of both have to be considered in formulating a neural mechanism to account for pitch discrimination.

[7] In discussing the effects of central nervous system lesions, we shall be concerned in this chapter with sensory capacity which can be demonstrated after the lesions; in many instances there is a loss of a learned discriminatory habit following central nervous system damage, but relearning occurs. See Chapter LXI for review of studies on the neural basis of learning.

[8] This is, of course, an oversimplified definition in view of the known interconnections among the many sub-systems within the central nervous system; it is, nevertheless, a convenient working definition for the present discussion.

[9] For a review of the problem of defining dimensions of sensation, see Boring (27).

From future experiments new kinds of information are needed to fill in the gaps which now exist. We need in particular to know more about: *a*) patterns of neural activity elicited by peripheral stimulation and *b*) effects of systematically varying patterns of nerve pathway or nerve center activity on discriminatory behavior.

INTENSITY DISCRIMINATION. In the very first experiments in which electrical signs of activity in sensory nerves were recorded successfully during stimulation of the sense organs supplied by the nerves, it was apparent that increase in intensity of stimulation leads to increase in rate of firing of nerve impulses. It was also noted that as intensity is increased, more nerve fibers are activated (3, 5).

Through the use of techniques designed to isolate single sensory nerve fibers and through the use of better methods of electrical recording, analysis of the responses in single first-order fibers of the visual (87), auditory (203), tactual (5, 6), kinesthetic (140–142), vestibular (133, 134) and taste (166) systems has now been accomplished. In all instances, a systematic relationship between strength of stimulus and frequency of nerve impulses has been found. The picture has been complicated, however, by the further finding that in all of these systems there are many fibers in the first order neurons in which a 'spontaneous' discharge occurs, i.e. a regular firing of nerve impulses occurs even when the end organ is not being stimulated. This phenomenon was noted by Adrian in his 1926 report (3) and again by Adrian & Zotterman (5); but they could not rule out the possibility that in the receptors of resting muscle or in tactual receptors not being intentionally stimulated, a mild degree of stimulation was taking place due to such factors as muscle tonus or skin tension. In other systems, e.g. vestibular, visual and auditory, it appears less likely that the spontaneous firing which has been observed (88, 133, 134, 203) can be accounted for in terms of mild external stimulation of receptor organs. A more likely explanation is that metabolic processes within the end organ give rise to the spontaneous discharges.

In addition to spontaneous discharge and the increase in frequency of discharge with increase in intensity of stimulation, another phenomenon has been observed in first order neurons of the vestibular and taste systems. Lowenstein & Sand (133, 134) have isolated single fibers from the ampullae of the semicircular canals of the ray and have found that these fibers fire spontaneously when the end organ is at rest, fire at an increased rate when the head is rotated towards the side of the semicircular canal from which a recording is being made, and fire at a rate below that of spontaneous discharge when the head is rotated in a direction away from the side of the canal being tested.

Pfaffman (167) has observed inhibition of spontaneous discharge in single fibers of the chorda tympani of the rabbit. The inhibition occurs when taste receptors are stimulated by weak solutions of sodium chloride; other substances such as potassium chloride and hydrochloric acid produce increased discharge.

While similar findings to those reported by Lowenstein & Sand for the vestibular system and by Pfaffman for taste have not been observed for first-order fibers of the other sensory systems, observations obtained from microelectrode recording in peripheral neurons one or more synapses removed from the end-organ receptors reveal a number of phenomena which must be taken into consideration in relating neural discharge rate to peripheral stimulus intensity.

In the optic nerve of the frog, Hartline (88) has described three types of nerve fibers, classified in terms of their responses to peripheral stimulation. Fibers of one type respond to onset of stimulations; after an initial burst of rapid activity, these fibers maintain a somewhat slower steady rate of response during the period of stimulation. A second type responds with a burst of impulses at onset and at cessation of stimulation but remains silent in between. Fibers of a third type fire only at cessation of stimulation.

Recording from cell bodies of second order neurons of the auditory nerve of the cat, Galambos & Davis (69, 70) have discovered single units which fire spontaneously in the absence of end-organ stimulation, at an increased rate during stimulation by tones of some frequencies, and at a decreased rate during stimulation by tones in a different part of the frequency range. Other fibers of the auditory system show only increased rate of discharge when the end organ is stimulated. No 'off' responses were reported by Galambos & Davis. Tasaki & Davis (205), recording with microelectrodes from second order auditory fibers in the guinea pig, failed to find fibers in which spontaneous discharge was inhibited by tonal stimulation. Tasaki (204) suggests that the difference between the results obtained by him and Davis and those reported earlier by Galambos & Davis for the cat may be due in part to difference in

size of electrodes used and to their placement in the cochlear nucleus. In the Tasaki & Davis study, the microelectrodes were sufficiently small to record intracellular potentials; those used by Galambos & Davis were larger and could only record extracellular potentials. Furthermore, Tasaki points out that he and Davis probably recorded from the ventral cochlear nucleus where there is an absence of cell bodies with long dendrites and consequently an absence of large external potential fields generated by the cell bodies when their surfaces are uniformly activated. Galambos & Davis, on the other hand, were more likely recording from the dorsal cochlear nucleus where there are many cells with long dendrites which can generate large potential fields around them. In unpublished experiments, Galambos & Tasaki report having observed "suppression of spontaneous discharges with submicroscopic electrodes inserted into the dorsal cochlear nucleus of the cat" (204).

With electrodes in the mitral cell layer of the olfactory bulb of the rabbit, Adrian (4) recorded the activity of single neural units and observed 'spontaneous' discharge in the absence of intentional stimulation and increase in discharge rate when the concentration of substance stimulating the olfactory receptors was increased.

Results for all the senses agree that, in addition to an increase in rate of impulse discharge in some units, increase in intensity of end-organ stimulation results in the excitation of more nerve fibers. There is also evidence that some sensory fibers have higher thresholds than others and are therefore activated only by high intensities of stimulation (69, 142, 167, 203).

Although the simple relationship between stimulus intensity and rate of neural discharge is complicated by such phenomena as spontaneous neural firing and increased rate of discharge in some neurons at the same time that rate is decreased in others, it seems a safe conclusion that if both frequency of discharge and increased number of fibers are considered, increase in intensity of end-organ stimulation is represented in the peripheral pathway of each sensory system by increase in total flow of nerve impulses.

For sensory centers in the brain stem and cerebral cortex, there is only limited and, for the most part, indirect evidence relating frequency of nerve impulses in individual nerve fibers and spread of response or number of nerve fibers activated as functions of peripheral stimulus intensity. It has been shown that increase in intensity of peripheral stimulation may result in increase in neural discharge in midbrain centers, but, as would be expected, the relation is not always a simple one. As in more peripheral centers and pathways, factors such as spontaneous discharge and its suppression by stimulation in some instances and different thresholds of excitation complicate the picture (65, 71, 73, 84, 106, 107, 178, 206, 208).

Studies of responses evoked at the cerebral cortex support the hypothesis that the total number of impulses arriving at higher neural centers is correlated with stimulus intensity. At threshold intensities of peripheral stimulation, a small evoked response can be recorded typically from a relatively limited region of the relevant cortical projection area of the deeply anesthetized preparation. As intensity is increased, the amplitude of the evoked response is increased and responses can be obtained from a wider expanse of cortex. Insofar as these changes can be taken as indicators of increased frequency of nerve impulses arriving at the cortex and of increase in number of projection fibers conveying response, then the evidence from examination of evoked cortical activity supports the hypothesis stated above (94, 123, 210). Investigations using microelectrodes to record responses of individual cortical units also provide evidence that with increase in intensity of peripheral stimulation more units are fired and in many units more impulses per second are elicited (11, 47, 56).

Establishing a relationship between intensity of stimuli applied to sense organs and the total flow of nerve impulses in the neural pathways and centers connected with these end-organs is an essential first step in discovering the neural basis of intensity discrimination, but it is not sufficient as an explanation. It is also necessary to relate neural activity to behavioral discrimination. As one example of an attempt to do this, Granit (82) has cited the studies of Enroth as evidence for the proposition that brightness discrimination in vision is directly related to total flow of nerve impulses in the visual system. Enroth recorded the response of single fibers of the optic nerve when the eye was stimulated by light at different flicker rates and different intensities. She counted the number of nerve impulses elicited by the last four flashes of light preceding and immediately following the point at which fusion was reached. When frequency of nerve impulses was plotted against flicker fusion frequency for a large sample of nerve fibers ('on' and 'off' type fibers both being

included), a linear relationship was found. Since the frequency at which flicker fusion occurs is proportional to the logarithm of the brightness of a flickering light, Enroth (and also Granit) make the inference that brightness is directly related to nerve impulse flow.

Experiments are yet to be done in which processes in sensory neural pathways and centers are controlled and manipulated directly while behavioral discriminations are observed. First steps in this direction have been taken by the utilization of implanted electrodes to record neural activity from or to stimulate neural centers in unanesthetized animals.

Another method, one almost as old as the history of scientific investigation of sensation, has given us valuable data about the parts of sensory systems which are necessary for different kinds of sensory discrimination and has, moreover, enabled us to make some inferences about the neurophysiological processes which underlie sensory discrimination. The method is that of testing discriminatory capacity in animals after selective ablation of neural centers or the transection of neural pathways. The validity of the results obtained by use of this method depends on a number of factors, particularly: *a*) the definition of appropriate neural 'units' to be rendered nonfunctional by ablation, *b*) the exactness of surgical procedures, *c*) the adequacy of pre- and postoperative methods of measuring discriminatory capacity and *d*) the accuracy with which the damage done surgically is evaluated post-mortem. [For a more complete discussion of the ablation method, see Neff & Diamond (156).]

The capacity to discriminate changes in intensity of stimuli applied to sense organs has been measured carefully by behavioral techniques in a variety of experimental animals before and after ablation of the sensory projection areas of all of the sensory systems. The visual and auditory systems have received the most careful attention and consequently the results for these systems are most complete. Tactual discrimination has also been measured in a number of studies. Due to difficulty in controlling stimulation and lack of adequate data on central pathways and centers, the remaining senses have been examined only in a few preliminary experiments.

The capacity to discriminate small changes in the intensity of light is affected very little or not at all by bilateral ablation of the cortical projection areas of the visual system. Discriminations of differences in intensity of visual stimuli have been measured in the rat (118), cat (194), dog (137, 223 225) and monkey (113, 114) after complete bilateral ablation of the visual cortex.[10] Klüver has shown for the monkey that postoperative discriminations are made on the basis of differences in total luminous flux rather than on differences in brightness (113, 114). While appropriate control tests were not made in the experiments done on other species, a parsimonious conclusion is that they also discriminate on the basis of differences in total luminous flux.

Discrimination of changes in sound intensity has been studied for fewer animal species, but for the cat, at least, evidence is fairly conclusive that capacity to discriminate small differences in intensity of sound remains after complete bilateral ablation of auditory cortex (144, 171, 181). Evidence from studies in which other kinds of discrimination were measured suggests that similar results might be predicted for the dog and monkey (74, 104, 131).

Only rather crude measures of capacity to make discriminations of differences in tactual and kinesthetic stimulation have been obtained in experimental investigations (9, 10, 15, 45, 160, 188, 232, 233). The evidence that is available supports the conclusion that, for these senses also, capacity to discriminate small changes in intensity remains after bilateral ablation of the cortical projection areas although thresholds, at least in weight-lifting tests, may be slightly raised (188).

Effects of transecting afferent pathways at subcortical levels or of destroying subcortical centers of the sensory systems have been studied in only a very few experiments. Experiments in the rat show a loss in capacity to make brightness discriminations after ablation of the pretectile region of the thalamus and the optic tectum in addition to bilateral ablation of the striate cortex (119). Raab & Ades (171) have reported that, although the difference thresholds are increased, the cat can make discriminations of intensity of pure tones after bilateral ablation of the inferior colliculi as well as of the auditory cortex. The experiments of Sjöqvist & Weinstein (193) show that kinesthetic discrimination of differences in intensity (weight-lifting test) can be made after bilateral section of the medial lemniscus and spino-

[10] In many early and even in some more recent studies, all of the visual projection areas as they would be defined at present were not ablated; or, from the anatomical data reported, it is impossible to evaluate the completeness of the ablations. In the studies cited there was an attempt at anatomical control, and in some cases at least in each study the visual cortex appears to have been completely removed or the radiations to it transected.

thalamic tract; again, there is a deficit in differential sensitivity.

Results of experimental investigations using animals as subjects can be supplemented by observations made in careful clinical studies of man. In the latter, of course, it is usually impossible to obtain measures of discriminatory capacity in the same subject both before and after central nervous system damage caused by injury or disease. Moreover, the exact extent of the lesion cannot be controlled nor, in most instances, accurately determined post-mortem. Nevertheless, what evidence there is tends to support the conclusions which may be drawn from animal studies, namely that intensity discriminations can be made after severe damage to cortical projection areas. As noted earlier (p. 1452), there is some question as to the degree of blindness which follows ablation of the visual cortex in man. The defect following damage to or removal of parts of the visual cortex is not one of complete blindness in a circumscribed part of the visual field with normal vision in all other parts. Some residual sensitivity to strong stimuli remains in the center of most scotomatous areas (112); while in those parts which appear normal on routine perimetry and in which acuity is normal, more subtle defects, such as increased local adaptation and reduced critical flicker frequency, may be observed (16, 207). In cases of scotomas resulting from cortical damage, it is difficult to control completely for the possibility of stimulating innervated parts of the retina by stray light; it is difficult to determine that all projection to a given cortical sector has been destroyed; and it is difficult to show that all projection fibers from a given retinal area have been destroyed by a cortical lesion.

Because of the inadequacy of post-mortem examination of extent of brain damage and, in most instances, the lack of carefully controlled visual tests, it is impossible to evaluate the results of studies in which total blindness has been reported after complete bilateral destruction of visual cortex or of radiations to the cortex. Retraining methods such as used in experimental animals have not been used. It still remains a possibility that human subjects with complete bilateral ablation of the visual cortex might, with the proper procedures, be trained to make discriminations to gross changes of intensity of a visual stimulus. The assumption is that more subtle kinds of visual cues must be attended to.

QUALITY DISCRIMINATION. Summarizing the evidence bearing upon the neural mechanisms of discrimination of different qualities within each of the senses is less straightforward than the similar review for intensity discrimination. Since it is difficult to arrive at a satisfactory definition of sensory quality, we shall accept the qualities which were listed by introspective psychology and which have been accepted quite generally by investigators studying problems of sensation. For vision, qualities of sensory discrimination refer to colors; for hearing, to tones of different pitch; for touch, to light touch, deep pressure, warmth, cold and pain; for taste, to characteristics such as sweet, sour, bitter and salty; for smell, to odors such as burnt, fragrant and putrid.

As we have seen, the extension of the specific nerve energy theory to account for discrimination of qualities of sensation within a given sense modality was an obvious step and was quickly taken by other investigators of Johannes Müller's time. The specific nerve energy doctrine implied that each sensory modality had its end organ and connecting neural pathways and centers. In extending the doctrine to account for sensory qualities, a search was made for receptors which were selectively excited by the physical stimulus conditions known from psychophysical studies to give rise to the qualitative attributes of sensation.

Helmholtz initiated a search (which has continued until the present) for color receptors in the retina and for separate neural paths and centers serving these receptors. Details of the consequences of this search are given in Chapters XXIX and XXX. To summarize briefly: two classes of receptors in the retina have been identified, rods and cones. These two classes of receptors are related to scotopic and photopic vision, but only the cones appear to function in color vision. There is no direct evidence that types of cones having different sensitivities to different parts of the visible color spectrum can be identified.

In recent years, the peripheral mechanisms of wavelength analysis have been studied carefully by Granit and his co-workers (53, 77–80, 82). (They are discussed by him in Chapter XXIX of this *Handbook*.) The results of single unit analysis of optic nerve fibers have been incorporated into the dominator-modulator theory of retinal physiology. The dominators are elements with a strength of discharge to light which simply reflects either the scotopic or photopic luminosity curve. They are the carriers of the Purkinje shift. The modulators, on the other hand, exhibit sensitivity to the various wavelength ranges not predicted by the luminosity functions. A major conclusion to be

drawn from this work is that information about the spectral composition of the stimulus is coded by the modulator mechanisms into both spatial and temporal patterns of optic nerve discharge.

None of the modulators in the cat has a separate retinal pathway. The high degree of neural convergence precludes the possibility that spectral information is coded on the basis of different pathways for different wavelength ranges. The experiments of Donner (53) support the notion that the coding is based largely on the temporal distribution of impulses in the optic nerve. Many 'on-off' fibers in the cat retina exhibit maximal spiking at one or another of three places in the time course of their discharge, the position of the maximum depending upon the wavelength, but not the intensity, of the stimulating light. In the cat, then, the modulator mechanisms utilize primarily the frequency code of the optic nerve discharge. "In animals well supplied with modulators, such as snakes, pigeons, and to some extent frogs, color reception is likely to be based on both 'topography' ('place' or 'local sign') carried by modulators and on specific frequency patterns" (82, p. 289). Unfortunately, similar experiments have not been done at the primate level, but the peripheral mechanisms are probably not essentially different from those of the forms studied.

On the basis of anatomical observations, LeGros Clark (39-41) proposed that color discrimination might be accounted for in part by a place or topographical principle. The lateral geniculate nucleus of primates is divided into six layers, three receiving fibers from the contralateral nasal hemiretina and three from the ipsilateral temporal hemiretina. Clark suggested that each layer transmits impulses from the modulators related to one of the three primary components of the trichromatic theory of color vision, six layers being needed to convey the impulses from the two eyes. The evidence presented by Clark to support his hypothesis has been criticized by Walls (215). The proposal must be regarded as a tentative one, needing further experimental confirmation. In other recent studies, a search has been made for electrophysiological correlates of color vision. Some evidence has been reported indicating that amplitude, latency and shape of responses evoked from the visual cortex vary with the color used in stimulating the eye (37, 122, 123, 135). The results reported to date are only suggestive. If these characteristics of central nervous system response do have a relation to color vision, it would appear advisable to explore them in the primate or in another mammal known to have good color vision rather than in the cat which has been shown to be deficient in color discrimination (44, 51, 143).

Studies of behavioral discriminations of color before and after the production of lesions in neural pathways and centers of the visual system provide almost no evidence that will help in formulating a hypothesis as to a neural basis of color vision. In the monkey, there is evidence that discrimination on the basis of color cannot be made after bilateral ablation of the visual cortex (115). In other animals such as the dog and cat, which have been used most often in behavioral studies of vision, experiments indicate that at best the intact animal has a very low order of color vision. As pointed out above in discussing electrophysiological investigations, such animals are questionable subjects for color discrimination studies.

Reports from the clinic, likewise, furnish very little additional information on the role of the visual cortex or of lower centers in color discrimination. Electrical stimulation of the striate areas in man gives rise to reports of visual sensations which include that of color (163, p. 143). Ablation of parts of the visual areas in man produces scotomas in which complete absence of color vision is usually reported.

The evidence, though it is limited, does not lend much support to an explanation in which color discrimination is accounted for on the basis of separate sense-organ and neural units for the separately discriminable colors. On the other hand, it still remains a possibility that there are a number of separate color receptors in the retina and that they maintain to some extent independent central nervous system connections. It is more probable that different colors are represented in the central nervous system by patterns of activity which vary with respect to temporal and spatial arrangement of neural activity in groups of neural units.

Helmholtz's extension of the specific nerve energy theory to account for pitch discrimination in hearing has met with greater success than the similar suggestion for color vision. His resonance theory of hearing proposed that sounds are analyzed by the cochlea in such manner that for each discriminable pitch, there is a separate receptor unit which is excited by a given frequency or narrow band of frequencies. (Cochlear processes are considered by Davis in Chapter XXIII and central auditory mechanisms by Ades in Chapter XXIV of this *Handbook*.) Although the original simple resonance principle of analysis has been proved inadequate, it is generally accepted that peripheral analysis does take place, that high tones excite receptors in the

base of the cochlea and that as frequency of the stimulus is lowered, the region of maximal excitation moves towards the apex. It is also generally agreed that the degree of cochlear analysis, particularly for low tones, is not sufficient to account for the fineness of pitch discrimination. If pitch discrimination depends upon a place principle, then neural processes must result in some 'sharpening' or 'channeling' so that frequencies that can be discriminated activate separate neural units. To demonstrate such sharpening in a sensory system, Békésy (20) has used a dimensional mechanical model of the cochlea with the tactual receptors of the forearm of a human subject serving as the receptor cells of the basilar membrane; the traveling waves which under stroboscopic light may be seen moving along the surface membrane of the model are felt by the subject as a vibratory stimulus applied to a fairly sharply localized region on the forearm. The phenomena demonstrated by Békésy's model imply that 'inhibitory' or 'suppressor' processes in the afferent nerve pathways from the skin result in a channeling of neural activity.

The fact that the impulses in peripheral and central neural pathways are synchronous in frequency with stimulating tones throughout a wide range of frequencies may also be used in accounting for pitch discrimination. Wever (220) has suggested that frequency of nerve impulses may provide the principal cue for discrimination of tones in the lower range, perhaps up to 400 cps; for intermediate frequencies, a combined place and frequency principle may operate (400 to 5000 cps) with place being of primary importance for the highest audible frequencies (above 5000 cps).

Several investigators have recently called attention to the long-known but often disregarded fact that there are at least two kinds of subjective experience which we tend to include under the single heading of pitch perception. For example, we perceive tones such as those produced by an oscillator or organ pipe and we say that one tone is higher or lower in pitch than another. We can also make similar judgements about sounds which have an intermittent, rougher, noisier characteristic; these sounds can be matched in pitch with pure tones but they are by no means identical to the observer (49, 125, 126, 146, 180). As Licklider (125) notes, not only are there two attributes of pitch sensation, there are also two characteristics of the physical stimulus for pitch, namely frequency and periodicity. He postulates two neural mechanisms to account for the two attributes of pitch sensation. One is the classical frequency analysis according to place; the second is a neuronal autocorrelation analysis based on periodicity. The latter operates only for frequencies in the lower range, perhaps up to 1000 cps.

There is not only conclusive evidence for frequency analysis in the cochlea but also for topographic projection of the cochlea in neural pathways and centers up to and including the auditory areas of the cortex (69, 71, 84, 94, 106, 107, 109, 124, 203, 205, 208, 210, 211, 227, 228). The fact of such projection does not necessarily mean that it provides the basis for pitch discrimination. As Lashley (120) has pointed out, the maintenance of systematic spatial organization from peripheral end organ to cortex may be the result of the mechanics of embryonic development. Wires may be strung side by side in a telephone cable, but messages sent over these wires may still be in a frequency code. Nevertheless, there remains the fact that in a system such as that formed by the auditory neural pathways, spatial arrangement of axons in tracts and of the cells upon which they end must inevitably play a role in determining the manner in which afferent events produce the efferent activity which eventually results in the final acts of sensory discrimination.

To the investigator searching for an explanation in neurophysiological terms of sense-quality discrimination, the rather beautiful picture of tonotopic organization in the auditory system is, at first, both reassuring and exciting, reassuring in that it suggests that a simple principle, spatial organization, may be fundamental for discrimination of a sensory quality and exciting because of the possibilities for experimental test.

When the experimental test is made, the results are disappointing, at least at first consideration. Complete bilateral ablation of the tonotopically organized auditory cortex produces little or no effect upon the capacity of experimental animals to discriminate changes in frequency of tones (36, 144, 156, 179). Of course, the tonotopic organization exists in subcortical centers and, as we have already seen, learned responses to sound cues can be made in the absence of all cortex; nevertheless, the results may seem somewhat surprising in view of the fact that the auditory cortex provides a better structural possibility for discrete spatial differentiation than lower centers which have a lesser number of nerve cells and consequently lesser possibilities of discrete connections. At least, it might be expected (if topographic organization is important in sense-quality discrimination) that the fineness of frequency discrimination might be altered by ablation of the auditory cortex.

Since the initial studies of Blix, Goldscheider and

von Frey, there has been a continuous search for special receptors subserving touch, deep pressure, cold, warmth and pain. (These are considered in detail in Chapters XVII through XIX of this *Handbook*.) The early discovery of 'spots' of special sensitivity on the skin encouraged the belief that each of these different qualities[11] has its own kind of receptor. In fact, a little evidence and considerable imagination led to the assignment of a particular type of receptor for each quality: Meissner's corpuscles for touch, Pacinian corpuscles for deep pressure, Krause end bulbs for cold, Ruffini cylinders for warmth and free nerve endings for pain. The results of experiments in which 'dissociation' of these separate sense qualities was produced by peripheral nerve section and regeneration (24, 29, 43, 58, 89, 117, 154, 177, 190, 209), or by procedures designed to produce temporary alteration of skin sensitivity, and the discovery that the qualities were selectively disturbed by spinal cord lesions (57, 86, 105, 197, 214, 221, 222), all added up to a quite convincing argument in favor of a place (or specific nerve energy) explanation of somesthetic qualities. Despite the bulk of evidence accumulated by researchers holding this point of view and despite many thousands of words written in support of the evidence, there were a few dissenters who cited phenomena difficult to account for by a place theory and who produced alternative theories and some evidence to support these theories (for details, see Chapter XVII). Particular credit must be given to Nafe (151–153); to Bishop (23); to Jenkins (103); and to Weddell, Sinclair, Lele and their collaborators (191) for questioning the adequacy of the evidence produced to support the explanation of discrimination of pain, touch, warmth and cold, simply in terms of a specific receptor and specific neural unit theory. It now seems clear that an adequate theory of discrimination of somesthetic qualities must recognize that the same receptor endings are stimulated by different kinds of stimuli and that discrimination of quality cannot be based upon events in separate sensory-neural units but only upon differences in temporal and spatial patterns of events in the same or in similar units (85, 91, 121, 192, 217–219, 229–231).

The possibility remains that at the spinal cord level there is some differentiation of the paths subserving the qualities of somesthesis. At the thalamic and cortical levels there is almost no evidence to suggest that the separate qualities are represented in spatially separate areas (187).

Studies of the effects of ablation of the cortical projection areas of the somesthetic system or of lesions in subcortical pathways and centers are, in comparison to similar studies for vision and hearing, relatively scarce and the quality of the evidence is less satisfactory because of the difficulty in adequately controlling the parameters of stimulation. In experimental investigations only the tactual and kinesthetic senses have been examined with any care. The kinds of deficits which occur are described in other sections of this chapter.

Early psychophysical studies of taste indicated that different spots or regions of the tongue were particularly sensitive to stimuli which produced the sensations of salty, sweet, bitter and sour. Whether these are the basic taste qualities, and the only ones, may be questioned. (See the discussion of taste by Pfaffmann in Chapter XX of this *Handbook*.) At least they are the ones most readily differentiated and named by the human subject not only under experimental conditions but in common experience. Attempts to identify receptors having structural characteristics which might indicate differences in function have met with no success. Nor has it been possible to explain satisfactorily on the basis of the chemical composition of a given substance the taste that it will produce.

When substances known to arouse the sensations of salty, sweet, sour and bitter are applied to the tongue of experimental animals, records of activity in single fibers of the nerves supplying taste receptors show that some fibers are activated by acid alone, others by acid or salt, and still others by acid or quinine (166, 167). Experiments by Kimura & Beidler (111) provide evidence that the same taste bud may be excited by chemical substances which in man are known to produce more than one quality of sensation. This kind of experimental analysis in peripheral units leads to the inference that in response to substances which produce separate taste qualities, patterns of neural impulses, which differ both spatially (different nerve fibers) and temporally (frequency in individual fibers) are transmitted to the central nervous system.

Electrical stimulation of the glossopharyngeal and chorda tympani have made possible the mapping of cortical areas for taste in the rat and cat (21, 159) although the possibility that these areas may be tactual areas for the tongue cannot be completely ruled out.

[11] Or modalities. Since the same principle of specific nerve energies has been used to account for the difference in quality and the difference in modality, it has made little difference to research whether touch, temperature and pain were classified as separate modalities or as separate qualities of somesthesis.

Bilateral ablation of the cortical areas for taste in the rat has been shown to result in a deficit in discriminatory ability (21). A similar deficiency in taste discrimination has been found in the monkey after bilateral ablation of the cortex of the anterior part of the island of Reil, the operculum and the anterior supratemporal plane (13). The cortical areas for taste in the monkey have not been defined by electrophysiological methods.

Of all the sensory systems the investigation of the olfactory system has been particularly unrewarding. (Present knowledge is summarized by Adey in Chapter XXI of this *Handbook.*) Schemes to classify stimuli which arouse sensations of odor have not been satisfactory even from a subjective standpoint. While man can discriminate different odors on a qualitative basis, there are no particular qualities which appear to be distinctive in the same sense that sweet, sour, salty and bitter are for taste. As in taste, substances which arouse similar sensations are not necessarily similar in chemical composition.

It is difficult to expose the sensory receptors for olfaction and also difficult to isolate and record from single neural units of the peripheral olfactory system. Adrian (4) has been successful in recording activity of units of the olfactory bulb and the results of his experiments are of special interest in that it appears that different patterns of response are elicited by different stimulating substances.

Lack of accurate knowledge of the central connections of the olfactory system, as well as inadequate control of the parameters of stimulation, has made impossible anything but the crudest kind of experimentation through the use of the ablation method. About all that can be said at present is that the only lesion which has been shown to have an effect upon capacity for olfactory discrimination is bilateral section of the olfactory tracts (7, 8, 200, 201).

SPACE DISCRIMINATION.[12] For man and for many of the higher mammals, the visual and somesthetic systems are usually thought of as being the senses of primary importance in discriminations involving the localization of objects in space. This is true; vision is the sense used in most instances for localization of objects at a distance; touch as well as vision, for objects near the body. The auditory system is of less importance. Sources of sound can be localized as to angular position with reasonable accuracy, although some confusions arise; only crude estimates can be made of distances. Considered not as a system providing accurate localization of objects in space but as a system which provides a background of information about environment, it may be argued that the auditory system is not of secondary importance in space discrimination. This function of auditory cues has been stressed by Ramsdell (172) and by Myklebust (150) in discussing the problems of the deafened individual.

Other sensory systems also play significant roles in space discrimination. Visual and tactual discriminations of space can be made because postural adjustment and orientation of the body are maintained. The kinesthetic and vestibular systems are essential for the maintenance of posture and orientation. Moreover, visual and tactual perceptions of distance and position of objects are in part at least learned; tactual and particularly kinesthetic cues are critical in this learning. The remaining sensory systems, taste and olfaction, do not, as far as we know, contribute significantly to space discrimination and will not be considered further in the present discussion.

At the periphery, visual and somesthetic space are represented as two-dimensional maps. Objects at a distance project upon the retina in an organized spatial pattern. Objects brought into contact with the body produce spatial patterns of excitation in the skin receptors.

Evidence from anatomical and electrophysiological studies shows clearly that for all species of animals that have been studied, there is topographic projection of the retina upon higher centers up to and including the cerebral cortex (22, 33, 34, 42, 138, 169, 170, 202). Likewise, for the somesthetic system, different regions of the body are topographically projected upon the cerebral cortex and this organization is maintained in pathways and centers intervening between skin and cortex (54, 55, 139, 149, 226).

In the auditory end organ, outer space is not represented by a spatial map. As we have seen (p. 1458), it is frequency of the sound stimulus that is represented spatially along the basilar membrane. Sounds at different angles from the axis through the two ears differ in their time of arrival, in their relative intensity and in their complexity at the end organs. Psychophysical studies (126) have shown that for tones of low frequency (1000 cps and below), time differences (time of arrival or phase) at the two ears provide the principal cues for space localization; intensity differences are more important for tones of high frequency (above approximately 4000 cps). There is a range of frequencies between 1000 and 4000

[12] For an interesting discussion of spatial and temporal events in the central nervous system as related to the space and time dimensions in the external world, see Davis (48). Space discrimination is discussed by Teuber, Chap. LXV, this volume.

cps for which localization is less accurate than for either lower or higher frequencies. For complex sounds, time, intensity and quality differences are all probably utilized. How time and intensity differences at the periphery are coded in neural centers is not as yet completely clear. A number of investigators during the past 30 years have suggested that these differences become place differences in the central nervous system, i.e. that auditory space is in some manner topographically represented in the brain (18, 19, 25, 102, 168). There is no experimental evidence to support this view, but it has not been carefully explored. In a series of experiments Rosenzweig and his co-workers (182–186) have recorded electrical responses at the cochlea, cortex, and inferior colliculus of the cat when activity in the auditory system is set off by clicks which are varied in intensity and in time of arrival at the two ears. They have found that the pattern of response recorded by a gross electrode at the cortex or the inferior colliculus varies systematically as a function of the interval separating two clicks successively presented, one to each of the ears. The cortical response also varies when the two clicks are presented simultaneously but one of less intensity than the other.

Because of methodological difficulties encountered in systematically exploring different regions of the body and in restricting stimulation to the appropriate receptors, there have been few attempts to discover the organization of the pathways from kinesthetic receptors to cortex. The electrophysiological experiments of Mountcastle *et al.* (148) have shown that stimulation of nerve fibers of muscle afferents or stimulation of receptors in the region of joints and tendons will evoke responses from somatic areas I and II of the cat cortex. Furthermore, although mapping was confined to the fore- and hind limbs, the topographic projection of these regions was approximately that of the cutaneous afferents. As Mountcastle and his collaborators noted, however, the receptors and nerve fibers stimulated in the experiment may have been those which mediate the sense of deep pressure or pain rather than muscle movement or position. (Rose & Mountcastle have reviewed this topic in Chapter XVII of this *Handbook*.)

Evidence for the central projection of the subdivisions of the vestibular end organs is still more meager than for the kinesthetic receptors. In any case, the vestibular end organ is not a space receptor in the same sense as the other systems described above. It signals direction of movement (linear and angular acceleration) and position of the head. It has always been a point of argument as to whether or not any direct sensory experience was aroused by excitation of the vestibular end organs and the consequent flow of nerve impulses to higher centers. From introspective analysis it seemed a likely possibility that the sensation aroused upon vestibular stimulation was not a direct one but only the awareness of eye movements, muscular contractions and relaxations in skeletal muscles, responses of stomach muscles, and other reflex actions known to be elicited by vestibular stimulation. Although it did not necessarily follow, this position was usually accompanied by the view that the vestibular system had no cortical representation. It now appears that different parts of the vestibular end organ may be projected to different but adjacent and overlapping areas of the cortex of the temporal lobe (12, 72, 108, 145, 187, 195, 196, 216). There is no obvious parallel here, however, with the visual and tactual systems in that for both of the latter, outer space is represented topographically on the cortex.

A number of behavioral studies have been made in which capacity for spatial discrimination has been examined before and after central nervous system lesions. After complete bilateral ablation of the visual cortex, rats (118), cats (194), dogs (137, 223–225) and monkeys (113, 114, 116) can make correct choices between two stimuli differing in luminous flux. The test procedures used in the experiments performed were designed to measure intensity discriminations, but they may be interpreted as indicating some degree of visual space localization in that the animals had to make a choice of two stimuli which were spatially separated, the positions of the two stimuli being reversed in a random order on successive trials. Since contour discrimination is absent in animals lacking a visual cortex, accurate visual localization of objects separated by different angular distances is obviously impossible. Ability to discriminate distance has not been carefully measured after visual cortex ablation but, again as would be expected in the absence of ability to discriminate contours, it appears to be lost; animals trained to approach a lighted door proceed until they make contact with their vibrissae or skin. One would infer that animals such as the rat, cat and monkey, after ablation of the visual cortex, perceive a two-dimensional world, a world without depth, without contours, differing only in brightness gradients or perhaps of uniform brightness at any given instant but changing when eye and head movements lead to increase or decrease in luminous flux.

In experiments involving ablation of the somatic areas of the cortex in animals, the tests used have not as a rule required localization of tactual stimulation of the skin. An exception is a study by Peele (160) who measured, among other things, localization of touch and pinprick. Unilateral ablations were made of Brodmann's areas 1 and 2, 3, 5 or 7 separately or of 1, 2, 5 and 7 together. Peele reported that localization of tactile and painful stimuli "was persistently impossible after all ablations." In other investigations, it has been shown that the monkey and chimpanzee show a deficit in ability to discriminate tactually between such objects as a cone and pyramid. Discriminations of this kind probably depend in part upon tactual localization. Ruch & Kasdon (187) in comparing effects of cortical ablation on placing and hopping reactions and on weight discrimination have suggested that the greater effect on the former may be due to the fact that spatial localization is to some extent required whereas it is not in weight discrimination.

Another kind of experimental evidence as to space localization for somesthesis comes from the experiments of Dusser de Barenne (54, 55). He showed that strychnine applied to the cortex of animals led to scratching at a particular part of the body or to hypersensitivity of an area of the skin. By observing the skin areas affected, he was able to produce maps of the sensory cortex similar to those obtained later by the evoked potential method. From Dusser de Barenne's experiments, it may be inferred that arousal of neural activity in a restricted part of the somatosensory cortex gives rise to sensations localized in a particular part of the body.

Although the evidence from animal studies is sparse, it tends to substantiate the more abundant evidence from clinical observations. Head & Holmes were the first to use the careful techniques of the psychophysics laboratory in the examination of patients with brain damage. Because they had early become convinced that one should look for different qualities of sensation which might be separably affected by cortical lesions, the observations made by Head & Holmes are particularly relevant here. Among other deficits in somesthetic sensation resulting from damage to the cortex of the parietal lobes, they did find in many cases disturbance in tactual localization (90, 96). One of the three main functions of the somatic cortex according to Head was "the appreciation of relationships in space."

Critchley (46) has recently summarized clinical research on the parietal lobes. He cites numerous studies in addition to those of Head & Holmes in which deficits in somesthetic localization have been observed after parietal lobe damage. Complete absence of localization of tactual, pain or temperature stimuli is not reported, but errors in accuracy of localization are often increased.

The findings of clinical studies in which the surface of the cortex has been explored by electrical stimulation provide a most convincing kind of evidence that topographical projection of the surface of the body upon the cerebral cortex is of functional significance in spatial discrimination. Penfield and his collaborators have shown that in unanesthetized patients stimulation of points in both postcentral and precentral gyri by mild electric current gives rise to reports of somesthetic experience (161–163). The sensations described by the patients are localized in particular regions of the body and a systematic relationship is found to exist between the points on the cortex excited and the parts of the body to which sensations are referred. The kinds of sensation which the patients report are, in most cases according to Penfield & Rasmussen (163), feelings such as numbness, tingling or electric shock. Feelings of movement in parts of the body also occur, but less frequently.

Partial loss in capacity to localize sound in space after ablation of auditory cortex has been found in experiments on the rat, dog and cat. The earlier experiments on the rat (164, 165) and dog (74) are difficult to evaluate because of incomplete anatomical information on locus and extent of lesions. It is clear from the studies on the cat (155, 157) that partial bilateral ablation of the auditory projection areas results in a decrement in performance in a discrimination requiring localization of sound in space.

A survey of the clinical literature on effects of temporal lobe damage in man does not bring to light much evidence bearing upon the problem of localization of sound in space. Accurate tests of ability to localize have usually not been made. A recent report by Longo *et al.* (132) suggests that temporal lobe lesions in man may produce disturbances in sound localization when the latter is measured carefully; they state that "cases with lesions involving the temporal lobe showed marked impairment of localization of sound in the contralateral auditory field while lesions in other areas of the cortex showed no such impairment."

For the kinesthetic and vestibular senses, studies have not been done in which spatial discrimination

was carefully measured before and after experimental ablations of neural structures. As mentioned above, disturbances in placing and hopping reactions occur after parietal lobe ablations; spatial cues are to some extent involved in these responses.

In clinical cases, loss of ability to recognize position of limbs and movements of the limbs in space has been stressed by Head & Holmes and others as a prominent symptom of damage to the somesthetic cortex.

PATTERN DISCRIMINATION. Except under the carefully controlled conditions of the laboratory, most sensory discriminations made by man or other higher animals are discriminations of changes in temporal and spatial patterns of physical events. Techniques have not yet been devised so that we can get a good picture of the complex neural activity aroused by patterns of end-organ excitation. However, in behavioral studies aimed at clarifying the role of higher centers of the central nervous system in sensory discrimination, patterns of sensory stimuli have often been used, both in experimental and clinical investigations.

In all animals that have been studied (rat, cat, dog, monkey and man), it has been found that capacity to discriminate visual patterns is permanently lost after bilateral total ablation of the visual cortex. Small remnants of the visual projection areas are sufficient to mediate discriminations of simple patterns. In the rat, Lashley (119) has estimated that pattern discrimination is not destroyed if an amount of cortex equal to about one sixtieth of the total is spared in the macular projection region. Deficiencies in visual pattern discrimination have been reported in some studies after ablation of preoccipital cortex (1, 2) and of association cortex in the parietotemporopreoccipital region (38).

Discrimination of tonal patterns has been studied by Diamond & Neff (52) in the cat and by Jerison & Neff (104) in the monkey. The sound patterns used in these experiments were temporal rather than spatial, i.e. they consisted of a change in the temporal sequence of pulsing tones. In the cat, complete bilateral ablation of the auditory projection areas I, II and Ep (areas defined by evoked potential mapping) led to total loss of capacity for pattern discrimination. A small remnant of auditory cortex permitted relearning of the pattern discrimination habit. That the loss after total ablation was a loss of capacity to recognize the patterning of the physical stimulus was shown by control tests which revealed that the same animals which could not do pattern discrimination could discriminate changes in frequency. Goldberg *et al.* (76) have also reported that ability to discriminate temporal patterns of tones is affected in the cat after bilateral ablation of insular-temporal cortex ventral to the region defined as auditory cortex by evoked potential mapping.

Considered only casually, the striking parallel between the visual and auditory systems with respect to cortical function in pattern discrimination may not at first be apparent. In the case of the visual system, we speak of a loss of capacity to discriminate spatial patterns; for the auditory system, a loss of capacity to discriminate temporal patterns. But, when we look more closely at the order of events in the central nervous system, it becomes clear that the spatial patterns at the retina and the temporal patterns at the basilar membrane become, in the peripheral nerve and in higher centers, patterns of nerve impulses which differ both in space and in time.

It is probably impossible to stimulate the retina in such a fashion that a pattern of nerve impulses is set off having only space, or place, differences. As Lashley has pointed out (120), even with tachistoscopic presentation of light stimulus, the aftereffects will likely produce a train of nerve impulses. Furthermore, if the activity in the first or second order neurons had only spatial patterning, it must inevitably have temporal patterning as well by the time it arrives at higher centers because of such factors as differences in conduction rate and differences in number of synapses crossed.

Similarly, temporal patterns of tones presented to the cochlea elicit not only a temporal sequence of events in the peripheral nerve but, at least when more than one tonal frequency is used, there will be spatial differences as well.

Capacity to discriminate tactual patterns has also been measured before and after cortical ablations. The experiments have been less adequate than those for vision and hearing, both from the standpoint of stimulus control and evaluation of the locus and extent of the experimentally placed lesions. Nevertheless, the results tend to support the evidence from visual and auditory experiments that the cortical projection areas play a critical role in discriminations of spatial and temporal patterns. Rats and cats show deficits in ability to discriminate differences in roughness after lesions of somatic areas I and II (232, 233). Monkeys are less able to discriminate forms such as pyramid versus cone by tactual cues (45). In man, likewise, discriminations of temporal and spatial patterns are severely affected by lesions of the parietal cortex (46, 90, 96).

*Relation of the Primary Sensory Systems to Other Systems*

In considering the neural mechanisms of sensory discrimination, our first emphasis has been on the structure and function of the main afferent systems leading from the peripheral sense organs to higher centers of the brain. Without knowledge of the sensory input, we cannot begin to talk about the neurophysiology of sensory discrimination. On the other hand, even with more exact and detailed knowledge of the main afferent systems than we now possess, we would still be far from an understanding of sensory discrimination. We must also consider the control of sensory input, the effects of activity of nonsensory systems on this input, and the manner in which the sensory input leads to motor response.

The living organism at any given moment is subjected to a variety of external stimuli which may act upon sense organs and arouse activity in sensory pathways. For the higher animals, behavior does not appear to be controlled simply by the total pattern of stimuli acting upon the sense organs. Careful observation of behavior leads to the inference that there is some control exercised over the sensory systems so that a systematic, not random, switching occurs, thus allowing the input of one sensory channel to guide the organism's responses at one point in time and another sensory channel to take over when appropriate. Or, perhaps, two or more channels may be open simultaneously or in such rapid alternation that the organism's actions are seemingly guided by a combined input. Psychologically, we talk about this control of sensory input under the heading of attention. Introspective psychologists found it necessary to add clearness or attensity as an attribute of sensation along with such other attributes as intensity, quality, extensity and duration. Physiologists, psychologists and neurologists studying brain function either in the experimental laboratory or in the clinic have also felt impelled, or at least have found it convenient, to use the concept of attention in describing the discriminatory behavior of both normal subjects and of subjects in which damage has been done to brain centers. (Attention is considered in Chapter LXIV by Lindsley in this *Handbook*.)

Any investigator who has tested the sensory discriminations of animals in a multiple choice situation is familiar with a pattern of behavior which often occurs when the discrimination is made very difficult. The experimental animal which has been making appropriate responses in less difficult discriminations suddenly appears to ignore the stimulus cues and adopts a position habit such as always selecting the stimulus on the right. This behavior can be described most readily by saying that the animal acts as if it does not 'attend' to the stimulus cues which the experimenter is presenting. This and other kinds of behavior which can, likewise, be conveniently described as deficits in attention are seen in animals with brain lesions in test situations in which the normal animal makes appropriate responses.

It is an old and well-substantiated finding that animals with frontal lobe ablation are deficient in ability to perform on a delayed response test (97, 98). (See Chapter LIV by Pribram in this *Handbook*.) Evidence from studies in which improvement in performance has been shown to occur if animals are tested in the dark or are given mild sedation suggest that the animal with frontal lobe lesions is more distractable; he is less able to maintain attention to the relevant cues in the test situation (136, 212).

Cats with lesions of the auditory cortex show a loss in ability to perform well in a test which requires localizing a sound in space and approaching the source of the sound in order to obtain a food reward (157). It has been suggested that the poor performance of these cats as compared with that of normal animals may be due in part to an inability to 'maintain attention' to the sound cues.

Not only in the reports of animal experiments but also in the clinical literature one finds many studies in which loss in some aspect of the ability to attend to sensory cues is described in patients who have suffered brain damage. Only a few examples will be cited here.

In their studies of the somesthetic sensibilities of patients with parietal lobe damage, Head & Holmes (90) describe a number of phenomena which they attribute to deficits in ability to attend to tactual stimulation. When a series of von Frey hairs is used to stimulate the skin in a region of the body affected by damage to the parietal lobe of the opposite side, the patient's responses are often quite erratic. He may respond frequently to stimuli as weak as those perceived on the normal side of the body but still fail to respond consistently to much stronger stimuli. Head offered the very interesting suggestion that such phenomena may be explained as defects of local attention. He thought of local attention, attention as related to a given sensory modality, as being a function of the cortical projection area of that modality. He recognized that there might also be a more general faculty of attention which would be altered by a variety of conditions affecting the brain.

In his summary of the literature on the function of the parietal lobes, Critchley has cited numerous examples from studies of his own and of other investigators (46). Phenomena observed during 'double stimulation,' usually of bilaterally symmetrical parts of the body, bring out in a clear fashion disturbances in sensory discrimination that can be most easily described as losses of capacity to attend. In some patients with a unilateral parietal lobe lesion such that the projection area of one hand is presumably damaged or destroyed, tests are made in which the affected and unaffected hands are stimulated simultaneously. The patient when blindfolded may report feeling an object only in the normal hand if two like objects are simultaneously placed in both hands. If the object is removed from the normal hand, the patient may then report the presence of an object in the affected hand. These and similar phenomena suggest that the deficit may be one in control of attention.

While such observations as those cited in the above examples were reported frequently, researchers in the field of sensory discrimination have been reluctant to deal directly with the problem of attention. This reluctance is understandable. It is due to a lack of knowledge of any neural system which might interact with the main sensory systems in such manner that appropriate control of input channels might occur. The discovery and clarification of the functions of the ascending reticular system and of the diffuse thalamocortical projection systems have not only dissipated the scientists' reluctance to face the problems of attention but has brought these problems to the fore. It is somewhat premature as yet to propose a neural theory of attention, but is is possible to cite a few experiments which bear upon the nature of the interaction between the specific and unspecific afferent systems.

It has been shown that in the brain stem the ascending reticular system (as discussed in Chapter LII of this *Handbook*) receives collaterals from the specific afferent pathways of the visual, auditory, somesthetic and vestibular systems (199). When the peripheral sense organs are stimulated, impulses are conducted therefore not only to the primary projection areas of the cortex via the specific afferent pathways but, after a longer latency due to delay in passage through many synapses in the reticular formation, to widespread regions of the cortex (198) as well as to the projection areas (100). If the specific afferent pathways are transected, sense-organ stimulation fails to produce the typical short latency evoked responses in the primary projection areas; activation of the EEG does occur in unanesthetized preparations (60, 62, 129, 130). In the anesthetized animal, the unspecific route via the reticular system appears to be blocked while the specific afferent pathways remain open; at the cortex, good evoked responses can be recorded from the primary projection areas during sense organ stimulation; activation of the EEG does not occur (61). These and other results suggest the hypothesis that interaction of the activity set off in the specific and unspecific systems must occur during sensory stimulation if the sensory stimulus is to be attended to and perceived clearly. That the cortex plays an important role in this interaction might be inferred from some of the evidence cited above. Lindsley, for example, has suggested that during sensory stimulation the activity arriving at the cortex via the unspecific system "sets the stage for the spreading and elaboration of the effects which reach the primary receiving areas. Its relative nonspecificity would favor this. If it acted by resetting excitability cycles of many neuronal aggregates so that a greater statistical availability of cellular units or patterns of units could at once be made possible, it should facilitate the chances of the primary message being received and transmitted in secondary or association areas and eventually leading to a response through the motor system" (127, p. 329).

A number of investigators (35, 99, 114, 127, 128, 147) have outlined in broad terms a theory which attempts to account, in neurophysiological terms, for a general arousal mechanism and a specific attention mechanism. The results of studies of experimental ablations in animals and of cortical damage in man support this notion of two systems, one having to do with maintenance of a general state of alertness, the other with control of direction of attention. In relation to the general alertness system, note should be taken of the proposal of Granit as to one possible significance of the spontaneous activity which has been recorded in peripheral sensory nerves. He suggests that the sense organs may serve as 'energizers'; the spontaneous activity in peripheral nerves feeds into the ascending reticular system via the collaterals from the main afferent pathways and helps to maintain a general state of wakefulness or alertness (82). This, as Granit points out, is only one possible role of the spontaneous activity. As we have noted above (p. 1454) inhibition as well as increase of spontaneous activity may occur during sense-organ stimulation. This kind of mechanism has greater information-handling capacity than one which is silent except during stimulation.

Another important recent development in neurophysiology which must be considered in relation to

both the specific and unspecific afferent systems is the discovery of evidence as to the functioning of corticofugal connections from the primary projection areas to subcortical centers of the specific afferent systems (31, 101, 143, 158, 175, 176), to the reticular formation (31, 59, 92, 101), and from both the reticular system and subcortical centers of the specific afferent systems to peripheral end organs (67, 79, 81, 83, 93, 110, 173, 174). For many years there has been some anatomical evidence for centrifugal fibers in the primary sensory pathways but until recently the evidence as to structural connections was rather sketchy and there was little or no functional evidence to indicate the possible physiological role of these recurrent tracts. (This field is the subject of Chapter XXXI by Livingston in this *Handbook*.)

Electrophysiological experiments have provided direct evidence that the input of the sensory systems may be controlled at a number of levels, including the peripheral end organ itself, by feedback through the centrifugal pathways. For example, control of muscle spindle discharge has been demonstrated by Granit & Kaada (83); of retinal discharge by Granit (81) and of cochlear discharge by Galambos (68). It appears that the centrifugal activity may affect sensory input at the end organ in several ways: *a*) by influencing the level of spontaneous discharge; *b*) by facilitating the peripheral excitatory process; or *c*) by inhibiting the peripheral excitatory process. Similar control may be exercised by higher centers upon those lower in the main afferent systems; by specific afferent centers on the reticular system; and by the reticular system on centers of the specific afferent systems.

The total picture of interacting specific and unspecific afferent systems and of centrifugal control of pathways within each system and between the two is one of great complexity but one which must be understood for a neurological theory of sensory discrimination. But this is still only a part of the total problem. By sensory discrimination we mean a discriminatory response to sensory stimulation. In the present chapter we have confined our attention to the input or sensory side of the picture. To account for motor response, at least two other subsystems within the central nervous system have to be considered: *a*) the centers and pathways which are involved in motivation of behavior and *b*) the motor system. Furthermore, the manner in which a connection is established between the sensory and motor systems is the most puzzling and perhaps the most important problem of all. From one viewpoint it can be regarded as the central theme of the subsequent chapters.

## REFERENCES


1. Ades, H. W. *J. Neuropath. & Exper. Neurol.* 5: 60, 1946.
2. Ades, H. W. and D. H. Raab. *J. Neurophysiol.* 12: 101, 1949.
3. Adrian, E. D. *J. Physiol.* 61: 49, 1926.
4. Adrian, E. D. *Acta physiol. scandinav.* 29: 5, 1953.
5. Adrian, E. D. and Y. Zotterman. *J. Physiol.* 61: 151, 1926.
6. Adrian, E. D. and Y. Zotterman. *J. Physiol.* 61: 465, 1926.
7. Allen, W. F. *Am. J. Physiol.* 128: 754, 1940.
8. Allen, W. F. *Am. J. Physiol.* 132: 81, 1941.
9. Allen, W. F. *Am. J. Physiol.* 147: 454, 1946.
10. Allen, W. F. *Am. J. Physiol.* 151: 325, 1947.
11. Amassian, V. E. *Electroencephalog. & Clin. Neurophysiol.* 5: 415, 1953.
12. Andersson, S. and B. E. Gernandt. *Acta oto-laryng.* Suppl. 116: 10, 1954.
13. Bagshaw, M. H. and K. H. Pribram. *J. Neurophysiol.* 16: 499, 1953.
14. Bailey, P. and G. von Bonin. *The Isocortex of Man.* Urbana: Univ. Illinois Press, 1951.
15. Bard, P. *Harvey Lectures* 33: 143, 1938.
16. Bay, E. *Brain* 76: 515, 1953.
17. Beare, J. I. *Greek Theories of Elementary Cognition.* Oxford: Clarendon Press, 1906.
18. Békésy, G. *Physik. Ztschr.* 31: 824, 1930.
19. Békésy, G. *Physik. Ztschr.* 31: 857, 1930.
20. Békésy, G. *J. Acoust. Soc. Am.* 27: 830, 1955.
21. Benjamin, R. M. and C. Pfaffman. *J. Neurophysiol.* 18: 56, 1955.
22. Biemond, A. *Experimenteel-anatomisch anderzoek omtrent de corticofugale optische verkindigan by aap en konijn.* Amsterdam: P. H. Vermuelen, 1929.
23. Bishop, G. H. *Physiol. Rev.* 26: 77, 1946.
24. Boring, E. G. *Quart. J. Exper. Physiol.* 10: 1, 1916.
25. Boring, E. G. *Am. J. Psychol.* 37: 157, 1926.
26. Boring, E. G. *A History of Experimental Psychology.* New York: Century, 1929.
27. Boring, E. G. *The Physical Dimensions of Consciousness.* New York: Century, 1933.
28. Boring, E. G. *Sensation and Perception in the History of Experimental Psychology.* New York: Century, 1942.
29. Bowden, R. E. M. Medical Research Council Special Report No. 282. London, 1954, p. 298.
30. Brazier, M. A. B. *J. Neurophysiol.* 20: 212, 1957.
31. Bremer, F. and C. Terzuolo. *J. physiol.*, Paris 45: 56, 1953.
32. Bromiley, R. B. *J. Comp. & Physiol. Psychol.* 41: 102, 1948.
33. Brouwer, B. *Deutsche Ztschr. Nervenh.* 89: 9, 1926.
34. Brouwer, B. and W. P. C. Zeeman. *J. Neurol. Psychopath.* 6: 1, 1925.
35. Buser, P. and A. Roger. *IV Congr. Internat. Electroencephalog. et Neurophysiol., Rapp., Discus. et Document.* Brussels: Acta Med. Belg., 1957, p. 417.

36. Butler, R. A., I. T. Diamond and W. D. Neff. *J. Neurophysiol.* 20: 108, 1957.
37. Chang, H. T. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 430, 1952.
38. Chow, K. L. and P. J. Hutt. *Brain* 76: 625, 1953.
39. Clark, W. E. Le Gros. *Nature, London* 146: 558, 1940.
40. Clark, W. E. Le Gros. *Docum. ophth.* 3: 57, 1949.
41. Clark, W. E. Le Gros and L. Chacko. *Nature, London* 160: 123, 1947.
42. Clark, W. E. Le Gros and G. G. Penman. *Proc. Roy. Soc., London. ser. B* 114: 291, 1934.
43. Cobb, S. *A.M.A. Arch. Neurol. & Psychiat.* 2: 505, 1919.
44. Cohn, R. J. *Neurophysiol.* 19: 317, 1956.
45. Cole, J. and P. Glees. *J. Neurophysiol.* 17: 1, 1954.
46. Critchley, M. *The Parietal Lobes.* London: Arnold, 1953.
47. Davies, P. W., A. L. Berman and V. B. Mountcastle. *Am. J. Physiol.* 126: 25P, 1954.
48. Davis, H. *Electroencephalog. & Clin. Neurophysiol.* 8: 185, 1956.
49. Davis, H., S. R. Silverman and D. R. McAuliffe. *J. Acoust. Soc. Am.* 23: 40, 1951.
50. Dennis, W. *Readings in the History of Psychology.* New York: Appleton, 1948.
51. De Voss, J. C. and R. Garson. *J. Animal Behav.* 5: 115, 1915.
52. Diamond, I. T. and W. D. Neff. *J. Neurophysiol.* 20: 300, 1957.
53. Donner, K. O. *Acta physiol. scandinav.* 21, Suppl. 72: 1, 1950.
54. Dusser de Barenne, J. G. *Quart. J. Exper. Physiol.* 9: 355, 1916.
55. Dusser de Barenne, J. G. *Proc. Roy. Soc.* 963: 272, 1924.
56. Erulkar, S. D., J. E. Rose and P. W. Davies. *Bull. Johns Hopkins Hosp.* 99: 55, 1956.
57. Foerster, O. and O. Gagel. *Ztschr. ges. Neurol. Psychiat.* 138: 1, 1932.
58. Franz, S. I. *J. Comp. Neurol.* 19: 107, 1909.
59. French, J. D., R. Hernández-Péon and R. B. Livingston. *J. Neurophysiol.* 18: 74, 1955.
60. French, J. D. and H. W. Magoun. *A.M.A. Arch. Neurol. & Psychiat.* 68: 591, 1952.
61. French, J. D., M. Verzeano and H. W. Magoun. *A.M.A. Arch. Neurol. & Psychiat.* 69: 505, 1953.
62. French, J. D., F. K. von Amerongen and H. W. Magoun. *A.M.A. Arch. Neurol. & Psychiat.* 68: 577, 1952.
63. Fulton, J. F. *Selected Readings in the History of Physiology.* Springfield: Thomas, 1930.
64. Fulton, J. F. *Physiology of the Nervous System.* London: Oxford, 1943.
65. Galambos, R. *J. Neurophysiol.* 15: 381, 1952.
66. Galambos, R. *Physiol. Rev.* 34: 497, 1954.
67. Galambos, R. *Fed. Proc.* 14: 169, 1955.
68. Galambos, R. *J. Neurophysiol.* 19: 424, 1956.
69. Galambos, R. and H. Davis. *J. Neurophysiol.* 6: 39, 1943.
70. Galambos, R. and H. Davis. *J. Neurophysiol.* 7: 287, 1944.
71. Galambos, R., J. E. Rose, R. B. Bromiley and J. R. Hughes. *J. Neurophysiol.* 15: 359, 1952.
72. Glebtzoff, M. A. *Arch. internat. physiol.* 50. 59, 1940.
73. Gernandt, B. *Acta physiol. scandinav.* 21: 73, 1950.
74. Girden, L. *Am. J. Psychol.* 53: 371, 1940.
75. Girden, E., F. A. Mettler, G. Finch and E. Culler. *J. Comp. Psychol.* 21: 367, 1936.
76. Goldberg, J. M., I. T. Diamond and W. D. Neff. *Fed. Proc.* 16: 47, 1957.
77. Granit, R. *Nature, London* 151: 11, 1943.
78. Granit, R. *J. Neurophysiol.* 8: 195, 1945.
79. Granit, R. *Sensory Mechanisms of the Retina.* London: Oxford, 1947.
80. Granit, R. *J. Neurophysiol.* 11: 239, 1948.
81. Granit, R. *J. Neurophysiol.* 18: 388, 1955.
82. Granit, R. *Receptors and Sensory Perception.* New Haven: Yale Univ. Press, 1955.
83. Granit, R. and B. R. Kaada. *Acta physiol. scandinav.* 27: 130, 1952.
84. Gross, N. B. and W. R. Thurlow. *J. Neurophysiol.* 14: 409, 1951.
85. Hagen, E., H. Knoche, D. C. Sinclair and G. Weddell. *Proc. Roy. Soc., London. ser. B* 141: 279, 1953.
86. Hamby, W. B. *J. Neurosurg.* 11: 378, 1954.
87. Hartline, H. K. *J. Cell. & Comp. Physiol.* 5: 229, 1934.
88. Hartline, H. K. *J. Opt. Soc. Am.* 30: 239, 1940.
89. Head, H. *Brain* 28: 99, 1905.
90. Head, H. and G. Holmes. *Brain* 34: 102, 1911–12.
91. Hensel, H. and Y. Zotterman. *J. Physiol.* 115: 16, 1951.
92. Hernández-Péon, R. and K.-E. Hagbarth. *J. Neurophysiol.* 18: 44, 1955.
93. Hernández-Péon, R. and G. Scherrer. *Fed. Proc.* 14: 229, 1955.
94. Hind, J. E. *J. Neurophysiol.* 16: 475, 1953.
95. Hines, M. *A. Res. Nerv. & Ment. Dis., Proc.* 13: 26, 1934.
96. Holmes, G. *Brain* 50: 413, 1927.
97. Jacobsen, C. F. *A.M.A. Arch. Neurol. & Psychiat.* 33: 558, 1935.
98. Jacobsen, C. F. *Comp. Psychol. Monogr.* 13: Serial No. 63, 1936.
99. Jasper, H. H. In: *Brain Mechanisms and Consciousness,* edited by J. F. Delafresnaye. Springfield: Thomas, 1954.
100. Jasper, H. H. and C. Ajmone-Marsan. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 493, 1952.
101. Jasper, H. H., C. Ajmone-Marsan and J. Stoll. *A.M.A. Arch. Neurol. & Psychiat.* 67: 155, 1952.
102. Jeffress, L. A. *J. Comp. & Physiol. Psychol.* 41: 35, 1948.
103. Jenkins, W. L. In: *Handbook of Experimental Psychology,* edited by S. S. Stevens. New York: Wiley, 1951.
104. Jerison, H. J. and W. D. Neff. *Fed. Proc.* 12: 237, 1953.
105. Kahn, E. A. and R. W. Rand. *J. Neurosurg.* 9: 611, 1952.
106. Katsuki, Y. and H. Uchiyama. *Proc. Jap. Acad.* 32: 67, 1956.
107. Katsuki, Y., H. Uchiyama, T. Watanabe and N. Maruyama. *Proc. Jap. Acad.* 32: 1, 1956.
108. Kempinsky, W. H. *J. Neurophysiol.* 14: 203, 1951.
109. Kennedy, T., N. Kiang and S. Sutton. *Am. J. Physiol.* 183: 634, 1955.
110. Kerr, D. I. B. and K.-E. Hagbarth. *J. Neurophysiol.* 18: 362, 1955.
111. Kimura, K. and L. M. Beidler. *Am. J. Physiol.* 187: 610, 1956.
112. Klüver, H. *Psychol. Bull.* 24: 316, 1927.
113. Klüver, H. *J. Psychol.* 2: 49, 1936.
114. Klüver, H. *J. Psychol.* 4: 383, 1937.
115. Klüver, H. *J. Psychol.* 11: 23, 1941.
116. Klüver, H. *Symp. Soc. Exper. Biol.* 7: 253, 1942.
117. Lanier, L. H. *A. Res. Nerv. & Ment. Dis., Proc.* 15: 437, 1934.

118. Lashley, K. S. *J. genet. Psychol.* 37: 461, 1930.
119. Lashley, K. S. *Symp. Soc. Exper. Biol.* 4: 454, 1950.
120. Lashley, K. S. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 529, 1952.
121. Lele, P. P., G. Weddell and C. M. Williams. *J. Physiol.* 126: 206, 1954.
122. Lennox, M. A. *J. Neurophysiol.* 19: 271, 1956.
123. Lennox, M. A. and A. Madsen. *J. Neurophysiol.* 18: 412, 1955.
124. Licklider, J. C. R. Doctoral Dissertation. Rochester: Univ. of Rochester, 1942.
125. Licklider, J. C. R. *Experientia* 7: 128, 1951.
126. Licklider, J. C. R. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951.
127. Lindsley, D. B. *Ann. Rev. Psychol.* 7: 323, 1956.
128. Lindsley, D. B. In: *Electrical Stimulation of the Brain*, edited by D. E. Sheer. Austin: Univ. Texas Press, 1958.
129. Lindsley, D. B., J. Bowden and H. W. Magoun. *Electroencephalog. & Clin. Neurophysiol.* 1: 475, 1949.
130. Lindsley, D. B., L. H. Schreiner, W. Knowles and H. W. Magoun. *Electroencephalog. & Clin. Neurophysiol.* 2: 493, 1950.
131. Lipman, E. A. *Am. J. Psychol.* 62: 215, 1949.
132. Longo, L. P. S., F. M. Forster and T. L. Lauth. *Neurology* 7: 655, 1957.
133. Lowenstein, O. and A. Sand. *J. Physiol.* 99: 89, 1940.
134. Lowenstein, O. and A. Sand. *Proc. Roy. Soc., London. Ser. B* 124: 256, 1940.
135. Madsen, A. and M. A. Lennox. *J. Neurophysiol.* 18: 574, 1955.
136. Malmo, R. B. *J. Neurophysiol.* 5: 295, 1942.
137. Marquis, D. G. *A. Res. Nerv. & Ment. Dis., Proc.* 13: 558, 1934.
138. Marshall, W., S. A. Talbot and H. W. Ades. *J. Neurophysiol.* 6: 1, 1943.
139. Marshall, W., C. N. Woolsey and P. Bard. *J. Neurophysiol.* 4: 1, 1941.
140. Matthews, B. H. C. *J. Physiol.* 71: 64, 1931.
141. Matthews, B. H. C. *J. Physiol.* 72: 153, 1931.
142. Matthews, B. H. C. *J. Physiol.* 78: 1, 1933.
143. Meyer, D. B., R. C. Miles and P. Ratoosh. *J. Neurophysiol.* 17: 289, 1954.
144. Meyer, D. R. and C. N. Woolsey. *J. Neurophysiol.* 15: 149, 1952.
145. Mickle, W. A. and H. W. Ades. *Am. J. Physiol.* 176: 243, 1954.
146. Miller, G. A. and W. G. Taylor. *J. Acoust. Soc. Am.* 20: 171, 1948.
147. Morrell, F. *IV Congr. Internat. Electro-encephalog. et Neurophysiol. Rapp., Discus. et Document.* Brussels: *Acta Med. Belg.*, 1957, p. 377.
148. Mountcastle, V. B., M. R. Covian and C. R. Harrison. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 339, 1952.
149. Mountcastle, V. B. and E. Henneman. *J. Neurophysiol.* 12: 85, 1949.
150. Myklebust, H. R. *Perkins School for the Blind Publication.* No. 19, 1956.
151. Nafe, J. P. *Am. J. Psychol.* 39: 367, 1921.
152. Nafe, J. P. *J. Gen. Psychol.* 2: 199, 1929.
153. Nafe, J. P. In: *A Handbook of General Experimental Psychology*, edited by C. Murchison. Worcester: Clark Univ. Press, 1934.
154. Napier, J. R. *Brain* 75: 147, 1952.
155. Neff, W. D., G. P. Arnott, and J. D. Fisher. *Am. J. Physiol.* 163: 738, 1950.
156. Neff, W. D. and I. T. Diamond. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958.
157. Neff, W. D., J. F. Fisher, I. T. Diamond and M. Yela. *J. Neurophysiol.* 19: 500, 1956.
158. Niemer, W. T. and J. Jimenez-Castellanos. *J. Comp. Neurol.* 93: 101, 1950.
159. Patton, H. D. and V. E. Amassian. *J. Neurophysiol.* 15: 245, 1952.
160. Peele, T. L. *J. Neurophysiol.* 7: 269, 1944.
161. Penfield, W. In: *Brain Mechanisms and Consciousness*, edited by J. F. Delafresnaye. Springfield: Thomas, 1954.
162. Penfield, W. and H. Jasper. *Epilepsy and the Functional Anatomy of the Human Brain.* Boston: Little, 1954.
163. Penfield, W. and T. Rasmussen. *The Cerebral Cortex of Man.* New York: Macmillan, 1950.
164. Pennington, L. A. *J. Comp. Psychol.* 25: 195, 1938.
165. Pennington, L. A. *J. Comp. Neurol.* 66: 415, 1957.
166. Pfaffman, C. *J. Cell. & Comp. Physiol.* 17: 243, 1941.
167. Pfaffman, C. *J. Neurophysiol.* 18: 424, 1955.
168. Piéron, H. *Année Psychol.* 23: 186, 1922.
169. Polyak, S. *A. Res. Nerv. & Ment. Dis., Proc.* 13: 535, 1934.
170. Polyak, S. and R. Hayashi. *Brain* 59: 51, 1936.
171. Raab, P. H. and H. W. Ades. *Am. J. Psychol.* 59: 59, 1946.
172. Ramsdell, D. A. In: *Hearing and Deafness*, edited by H. Davis. New York: Murray Hill, 1947.
173. Rasmussen, G. L. *J. Comp. Neurol.* 84: 141, 1946.
174. Rasmussen, G. L. *J. Comp. Neurol.* 99: 61, 1953.
175. Rasmussen, G. L. *Anat. Rec.* 115: 361, 1953.
176. Rasmussen, G. L. *Am. J. Physiol.* 183: 653, 1955.
177. Rivers, W. H. R. and H. Head. *Brain* 31: 323, 1908.
178. Rose, J. E. and V. B. Mountcastle. *Bull. Johns Hopkins Hosp.* 94: 238, 1954.
179. Rose, J. E. and C. N. Woolsey. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958.
180. Rosenblith, W. A. Progress Report II (PNM-6), Psycho-Acoustic Laboratory, Harvard University, 1947.
181. Rosenzweig, M. R. *Am. J. Psychol.* 59: 127, 1946.
182. Rosenzweig, M. R. *Am. J. Physiol.* 167: 147, 1951.
183. Rosenzweig, M. R. *J. Comp. & Physiol. Psychol.* 47: 269, 1954.
184. Rosenzweig, M. R. and A. H. Amon. *Experientia* 11: 498, 1955.
185. Rosenzweig, M. R. and W. A. Rosenblith. *Psychol. Monogr.* 67: No. 13 (Whole No. 363), 1953.
186. Rosenzweig, M. R. and E. J. Wyers. *J. Comp. & Physiol. Psychol.* 48: 426, 1955.
187. Ruch, T. C. In: *Textbook of Physiology*, edited by J. F. Fulton. Philadelphia: Saunders, 1955.
188. Ruch, T. C. and J. F. Fulton. *A. Res. Nerv. & Ment. Dis., Proc.*, 15: 289, 1935.
189. Scholl, D. A. *The Organization of the Cerebral Cortex.* London: Methuen, 1956.
190. Sharpey-Schafer, E. *Brain* 50: 538, 1927.
191. Sinclair, D. C. *Brain* 78: 584, 1955.
192. Sinclair, D. C., G. Weddell and E. Zander. *J. Anat.* 86: 402, 1952.

193. Sjöqvist, O. and E. A. Weinstein. *J. Neurophysiol.* 5: 69, 1942.
194. Smith, K. U. *J. genet. Psychol.* 51: 329, 1937.
195. Spiegel, E. A. *J. Nerv. & Ment. Dis.* 75: 504, 1932.
196. Spiegel, E. A. *A.M.A. Arch. Neurol. & Psychiat.* 31: 469, 1934.
197. Spiller, W. G. and E. J. Martin. *J.A.M.A.* 58: 1489, 1912.
198. Starzl, T. E. and H. W. Magoun. *J. Neurophysiol.* 14: 133, 1951.
199. Starzl, T. E., C. W. Taylor and H. W. Magoun. *J. Neurophysiol.* 14: 479, 1951.
200. Swann, H. G. *J. Comp. Neurol.* 59: 175, 1934.
201. Swann, H. G. *Am. J. Physiol.* 111: 257, 1935.
202. Talbot, S. A. and W. H. Marshall. *Am. J. Ophth.* 24: 1255, 1941.
203. Tasaki, I. *J. Neurophysiol.* 17: 97, 1954.
204. Tasaki, I. *Ann. Rev. Physiol.* 19: 417, 1957.
205. Tasaki, I. and H. Davis. *J. Neurophysiol.* 18: 151, 1955.
206. Tasaki, I., E. H. Polley and F. Orrego. *J. Neurophysiol.* 17: 454, 1954.
207. Teuber, H. L. and M. B. Bender. *Fed. Proc.* 7: 123, 1948.
208. Thurlow, W. R., N. B. Gross, E. H. Kemp and K. Lowy. *J. Neurophysiol.* 14: 289, 1951.
209. Trotter, W. and H. M. Davies. *J. Psychol. u. Neurol.* 20: 2, 1913.
210. Tunturi, A. R. *Am. J. Physiol.* 141: 397, 1944.
211. Tunturi, A. R. *Am. J. Physiol.* 160: 395, 1950.
212. Wade, M. *J. Neurophysiol.* 10: 57, 1947.
213. Walker, A. E. *The Primate Thalamus.* Chicago: Univ. Chicago Press, 1938.
214. Walker, A. E. *A.M.A. Arch. Neurol. & Psychiat.* 43: 284, 1940.
215. Walls, G. L. *Univ. Calif. (Berkeley) Publ. Physiol.* 9: 1, 1953.
216. Walzl, E. M. and V. B. Mountcastle. *Am. J. Physiol.* 159: 595, 1949.
217. Weddell, G. *Ann. Rev. Psychol.* 6: 119, 1955.
218. Weddell, G., W. Pallie and E. Palmer. *Quart. J. Microsc. Sc.* 95: 483, 1954.
219. Weddell, G., D. A. Taylor and C. M. Williams. *J. Anat.* 89: 317, 1955.
220. Wever, E. G. *Theory of Hearing.* New York: Wiley, 1949.
221. White, J. C. *A.M.A. Arch. Neurol. & Psychiat.* 71: 1, 1954.
222. White, J. C. and W. H. Sweet. *A.M.A. Arch. Neurol. & Psychiat.* 67: 315, 1952.
223. Wing, K. G. *Am. J. Psychol.* 59: 583, 1946.
224. Wing, K. G. *Am. J. Psychol.* 60: 30, 1947.
225. Wing, K. G. and K. U. Smith. *J. Exper. Psychol.* 31: 478, 1942.
226. Woolsey, C. N., W. H. Marshall and P. Bard. *Bull. Johns Hopkins Hosp.* 70: 399, 1942.
227. Woolsey, C. N. and E. M. Walzl. *Bull. Johns Hopkins Hosp.* 71: 315, 1942.
228. Woolsey, C. N. and E. M. Walzl. *Am. J. M. Sc.* 207: 686, 1944.
229. Zander, E. and G. Weddell. *J. Anat.* 85: 68, 1951.
230. Zotterman, Y. *J. Physiol.* 95: 1, 1939.
231. Zotterman, Y. *Ann. Rev. Physiol.* 15: 357, 1951.
232. Zubek, J. P. *J. Comp. & Physiol. Psychol.* 44: 339, 1951.
233. Zubek, J. P. *J. Neurophysiol.* 15: 401, 1952.

CHAPTER LXI

# The neural basis of learning

ROBERT GALAMBOS — *Department of Neurophysiology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.*

CLIFFORD T. MORGAN — *Department of Psychology, The Johns Hopkins University, Baltimore, Maryland*

CHAPTER CONTENTS



## INTRODUCTION

WE ARE CONCERNED in this chapter with what takes place in the nervous system during learning, and our goal is a precise description of its mechanisms. It will however become apparent as we proceed that while

relevant data abound in profusion, these often do not fit together in an orderly pattern, and they sometimes raise more questions than they answer. Besides this, the available methods for studying learning are frequently inadequate, and the ones best suited to the task have not been in use long enough to fulfill their promise. We will therefore be able to provide only a partial description of the mechanisms, this being derived from a statement of the problems as we see them, a summary of the data obtained by various methods and a discussion of some of the possible ways in which the nervous system functions in learning.

The study of the neural basis of learning is interdisciplinary; it draws on the facts and methods of a number of different fields. Experimental psychology, the discipline most directly charged with precisely defining the behavior called learning and conditioning, has made a substantial contribution, and familiarity with its techniques and terminology is required for any serious student of learning. For this reason, we devote the next section to 'Psychological Methods and Terms.' The several biological sciences, and particularly neuroanatomy, neurophysiology and biochemistry, are also heavily represented in the work on learning. What they offer in the way of methods and facts at the present time appears in the sections 'Ablation Studies,' 'EEG Correlates,' 'Brain Stimulation' and 'Psychopharmacology.' From a study of this material, the reader will be prepared, we trust, for the theoretical explanations for learning that are treated in the final sections.

But first a word about the references. Material published after June 1957 has not been cited with a few notable exceptions. The selected list here was chosen furthermore so that the reader could, by consulting their bibliographies, uncover practically everything known about the problem. We feel fairly certain of this with respect to the western literature despite the absence of a single modern German citation. The Russian and eastern European literature is another matter. The language difficulty here has been formidable, and we have worked either from brief summaries of obviously large research programs under way for many years, or from the translation of as few as one paper in a much larger series by the same author. Besides this, our Eastern colleagues in many instances approach learning problems in an interestingly different way from our own, and we are not entirely sure that, as reporters, our rendering of their facts and conclusions has always been wholly accurate. Certainly our report is not complete, much as we would have liked it to be.[1]

## PSYCHOLOGICAL METHODS AND TERMS

Although philosophers and scientists have long speculated about the nature of learning and have observed it in pets, zoo animals, children and fellow men, the first systematic observations of learning and memory were made by Ebbinghaus in 1885 (55). With nonsense syllables, which he invented, he carefully measured the course of memorizing and forgetting in human subjects. Then in 1906 Pavlov described (in English) his now famous discovery of the conditioned reflex, describing various factors governing its acquisition and extinction (180). About the same time, the maze was first employed for the measurement of learning in animals (221); and the problem box, in which an animal must discover through trial and error the solution to a problem, was used for a similar purpose (235). Thus were launched the two general kinds of methods, the conditioning method and the trial-and-error method, which have since provided the great bulk of information about learning and the various factors that affect it. It is necessary to have a clear understanding of these psychological techniques and the terminology that goes with them before turning to the neural correlates of learning and conditioning.

### *Conditioning*

As Pavlov used the term, 'conditioning' applied to a situation in which two kinds of stimuli are presented to an animal. One stimulus, called the 'unconditioned stimulus' (US), is any stimulus that evokes some definite response, called the 'unconditioned response' (UR), without any prior learning. In Pavlov's case, the US was food and the UR was salivation. Another stimulus, the 'conditioning stimulus' (or after learning has occurred, the 'conditioned stimulus' or CS), is one that prior to learning evokes no significant response. In many of Pavlov's experiments, this was a bell. By pairing the CS and the US, the one presented just before the other, and doing this for a number of trials,

[1] Our concern on this point has been considerably allayed by the publication by Rusinov & Rabinovich (211) of an admirable brief summary of much material relevant to this chapter.

Pavlov observed that the CS (the bell) came to evoke the UR (salivation) which he now called the 'conditioned response' (CR). This Pavlovian method of studying learning has in recent years been called 'classical conditioning' or conditioning of the 'first type.' We shall refer to it as Type I conditioning.

Type I conditioning procedures were subsequently modified by several investigators so as to employ a noxious stimulus, usually a shock applied somewhere to the skin of an animal, as the US. In this case an animal is presented with a CS (light or bell) followed by a shock (US), but only if the animal fails to make some specified response like lifting its leg (CR). In the United States, this conditioning procedure is usually called 'avoidance conditioning,' while others refer to it as defensive conditioning or conditioning of the 'second type.' Along with many others we shall call it Type II conditioning. Since what the subject does in the Type II procedure is instrumental in avoiding shock, it falls into the more general category of 'instrumental conditioning'—a term suggested by Hilgard & Marquis (98). There is evidence, however, that avoidance conditioning also involves the classical conditioning of autonomic reactions and consequently is not purely instrumental. Skinner's 'operant conditioning,' described in the paragraph below, is a better example of instrumental conditioning. Pavlov's classical conditioning is not instrumental because the animal's response (salivation) has nothing to do with whether or not the unconditioned stimulus (food) is presented.

Many years later, Konorski (121, p. 418) and Skinner (220) applied the term conditioning to a still different learning procedure. They put hungry rats in a box and delivered a pellet to them each time they pushed a lever. In this case, food was the US and pushing the lever became the CR. This situation differs, however, from both Pavlovian and avoidance conditioning in that: *a*) it contains no specifiable CS and *b*) the CR (pushing the lever) is not originally a UR to the food (US). For this reason, Skinner called it 'operant conditioning' in contrast to the first two kinds of conditioning, which he called 'respondent conditioning.' However, since the animal's response is instrumental in obtaining the food (US), this learning procedure must also be classified as a form of instrumental or Type II conditioning.

*Trial-and-Error Learning*

Skinner's Type II procedure, however, does not differ in principle from other learning methods that have been called 'trial and error.' Thorndike's cat in a puzzle box (235) indeed must do practically the same thing as Skinner's rat, namely push a latch to get out of a box to reach food. Similarly, animals required to run through a maze to receive a food reward must learn to make a number of turns correctly to reach the goal of food. Although the animal must make a series of responses, rather than just one, these are still instrumental responses which, like the rat in Skinner's box, are not themselves UR's and are not evoked by any identifiable CS's. Hence, it is only a matter of convention, not one of fundamental difference, to call maze learning and learning in puzzle boxes trial-and-error learning while calling Skinner-box learning conditioning.

*Perceptual Learning*

In addition to the learning studied in Type I and Type II procedures, organisms also can learn something about the relation of stimuli and of objects in their environment without necessarily making any overt responses. The general name for such learning is 'perceptual learning' because it involves a change in the perception of the environment. For our purposes two varieties of such learning may be distinguished, although there are others that need not be mentioned.

One is 'sensory-sensory learning.' In this case, one stimulus becomes associated with another by being regularly paired with it. An auditory stimulus, for example, might be presented immediately preceding a visual stimulus. The learning that occurs in such a procedure is not immediately available for scientific study because it does not involve a response. However, by conditioning some response to one of the paired stimuli and then testing with the other stimulus, one can establish that sensory-sensory learning actually takes place because the test stimulus evokes a response with which it has not previously been paired (23). By use of electrical methods of recording brain changes during learning, which will be described later, it is possible to measure changes in sensory-sensory learning directly.

Another kind of perceptual learning is that which is commonly called 'insight.' Its central feature is that the organism learns suddenly and without trial-and-error responses, as emphasized by Köhler (119). By attending to a problem and perceiving the relationships in it, the organism gains insight into its solution. Since we do not yet have any appreciable information

about the neural correlates of such learning, insight will not be discussed further in this paper.

Psychologists have sometimes tried to include perceptual learning with Type I or Type II learning. Many other schemes for classifying learning have been proposed, and considerable research and much controversy have revolved around them. There is no reason to go into these matters here, but the interested reader can delve into them by referring to excellent recent sources (45, 96, 97, 224, 236, 237). For our purposes, it is well to keep in mind the distinction between Type I and Type II learning procedures since the neural correlates of the learning phenomena associated with them are sometimes different.

### *Phenomena Related to Learning*

In addition to the three general classes of learning, there are three important phenomena closely related to learning that nevertheless differ in certain respects from what we ordinarily consider to be learning. One is 'habituation' (236, p. 388), the gradual waning of a response in the presence of continued stimulation (not to be confused with 'extinction' which will be discussed below). Fire a gun and it at first startles or excites the organism. Upon the repetition of such stimulation, however, the organism makes less and less response to it. Similarly, a dog placed in a harness is at first excitable and restless, but in time it settles down and becomes habituated to the situation.

Another related phenomenon is 'sensitization' (98, p. 41). This is an increase in responsiveness to a stimulus because of prior excitement by another stimulus. Shock an animal a few times and it is much more likely to respond excitedly to a bell or light than it would normally.

Still a third phenomenon, recently studied in some detail by ethologists, is 'imprinting' (200, 236–238). This is a relatively rapid 'learning' that takes place optimally at a certain time in the growing organism. A duckling exposed at a particular time after hatching to the call of the mother duck follows her thereafter, since imprinting develops relative to her. One can, however, experimentally evoke imprinting by the duckling relative to any other source of moving sound. This is a permanent change in the behavior of the organism and thus qualifies as learning, yet it involves so far as we know neither an unconditioned stimulus nor any instrumental response and hence is not quite like any of the three basic classes of learning.

REINFORCEMENT AND EXTINCTION. Both Type I and Type II learning require a 'reinforcement.' In classical (Type I) learning, the reinforcement is the US: in instrumental (Type II) learning, it is the reward or punishment that follows some specified response. The process of providing the reinforcement, it should be noted, is also called 'reinforcement.'

After a subject has learned a habit, the experimenter can institute an 'extinction' procedure. This is the omission of the reinforcement while maintaining all other aspects of the training routine. In Type I conditioning, extinction consists in presenting the CS without the US: in Type II learning, it consists of presenting the CS (in avoidance conditioning) or of permitting the animal to make its learned responses (in a Skinner box, puzzle box or maze) without providing any reward for such responses. The result of an extinction procedure is, of course, an increasing tendency for the organism not to give the CR until eventually the organism is not responding at all. This process, like the procedure, is also called 'extinction.'

Extinction is to be distinguished from 'forgetting' and its converse 'retention.' Forgetting is a diminution in the tendency to respond in the absence of further training or of experimental extinction. Teach an animal some particular response, rest him for a few days (or even hours) and he is likely to forget in some degree what has been learned. A few more reinforcements will be required before the animal again responds as consistently as it did at the end of the learning trials. The usual measure of such forgetting, however, is not the amount forgotten, but rather what is retained. If, for example, an animal was responding correctly 100 per cent of the time at the end of a series of learning trials, and then responds only 70 per cent of the time when tested after 2 weeks of rest, we say that the retention was 70 per cent. In neurophysiological studies of learning, we are interested not only in the neural basis of acquisition of learned responses but also in the brain events explaining retention of things previously learned. It sometimes happens, as we shall see, that acquisition and retention are separately affected by alterations in neural structure and functioning.

DISCRIMINATION. By a simple modification in learning procedure, one can study the acquisition and retention of a 'stimulus discrimination.' This is done by presenting two (or more) stimuli and reinforcing one but not the other. An animal will, for example, acquire a conditioned discrimination between the sounds of a bell and a metronome if the bell only is reinforced

with food (in salivary conditioning) or with shock (in avoidance conditioning). Responses eventually appear of course, to the bell but not to the metronome. It is possible to set up a still more complex discrimination between two stimuli. One might shock the left leg, for example, if a dog does not lift it upon hearing the bell, but shock the right leg if he does not lift that one upon hearing the metronome. In this case, a conditioned differential response is learned.

In differential conditioning procedures, the reinforced stimulus is known as the 'positive stimulus' and the one not reinforced is the 'negative stimulus.' On the other hand, the response the subject is trained not to make is regarded as being inhibited, and when the subject learns not to respond to the negative stimulus, the subject is said to have developed a 'conditioned' or 'internal inhibition.' Furthermore the response made to a positive stimulus may be called an 'excitatory reflex' while the response that is not made to a negative stimulus may be termed an 'inhibitory reflex.' These procedures and terms just described are most in vogue among the Russian and Pavlovian workers.

American psychologists, on the other hand, in general prefer to develop discriminations in animals by using 'avoidance conditioning' and 'discrimination learning' methods. In using 'avoidance conditioning' to set up a discrimination, some stimulus, say a tone of 1000 cycles, is presented continuously and the animal does not respond to it. When the tone is changed, however, say to 1020 cycles, the animal must learn to lift its paw (or run from one end of a box to another) to avoid shock. It is the change in the signal to which the animal is conditioned to respond.

In the type II situations, discrimination learning is actually another type of trial-and-error learning. The animal is presented with two stimuli and required to choose between them. Animals can be trained to make such choices by rewarding correct responses with food and punishing incorrect ones with shock. Many such techniques for discriminative learning, however, involve only reward, not punishment.

In the study of learning, it is often desirable to have problems of such difficulty that they tap the 'higher mental processes' of the animal—imaginal and ideational processes of the kind human beings use in language and thinking. For this purpose, the discrimination technique just described can be altered so that the animal must make a 'delayed response.' In this, the animal is presented with two stimuli, shown which one is correct and then is forced to wait for some interval, usually 10 sec. or more, before being permitted to make a choice. The position of the correct stimulus must of course be varied from trial to trial or the problem is no more than one of making a simple discrimination. Primates solve this kind of problem much more readily than do subprimate animals. The ability also depends, as we shall see, on the functioning of certain neural structures.

OTHER METHODS. One of the earliest devices to be employed in learning studies was the maze. Its chief advantage is that it can be varied in difficulty from a simple T, in which the animal makes one single choice, to extremely complicated patterns entailing 20 or 30 choices in a series. Mazes can also be planned in such a way as to constitute very difficult problems that can be solved only by using 'higher mental processes.'

Some of the more recent techniques for studying behavior are the so-called operant (Skinnerian) methods. These are Type II procedures that permit extremely delicate objective measures of the learned responses, the central correlates of which are our chief concern; for this reason we may expect to see them used increasingly. As an example of the niceties of the technique, consider the following (217). Rats can be taught to press a lever to turn off a shock that would otherwise be delivered to the feet. If a clock in the circuit determines that the shocks will be delivered every 20 sec. unless the lever is pressed (in which case the clock is reset to zero), the rat soon learns to space its responses reasonably accurately at nearly 20-sec. intervals. This learned 'timing behavior' is stable over many hours and from day to day. Automatic recording of the responses frees the experimenter from many unrewarding features of experimentation while at the same time providing a clear objective account of the ongoing behavior. The reader interested in this technique will wish to consult Ferster & Skinner (60).

*Summary*

This account of methods and terms used in the study of learning is necessarily quite brief. Learning has been studied in literally hundreds of other ways. We have selected only those terms, methods and concepts that provide the necessary background for the data to be presented on neural correlates of learning. For a more detailed discussion of methods, the reader should consult Hilgard's chapter in the *Handbook of Experimental Psychology* (96) and other useful sources of information (98, 170). For a treatment of the phenomena and concepts of learning, see Deese (46),

Hilgard (97), Hilgard & Marquis (98), McGeoch & Irion (153), Pavlov (181–183) and Konorski (120, 121).

## ABLATION STUDIES

The literature contains so many studies of the effects of damage to the brain upon learning and retention that any selection such as this one will provide limited coverage at best. This section attempts to summarize general trends by citing what are believed to be the most significant articles. More extensive treatments of the subject may be found in Morgan & Stellar (163), Morgan (161), Milner (157), Chow & Hutt (41), and in the chapters on physiological psychology appearing regularly in *Annual Review of Physiology* and *Annual Review of Psychology*. It is also considered in the chapters in this *Handbook* dealing with various regions of the brain, especially Chapters LIV and LXVII.

### *Spinal Conditioning*

It still is an open question whether the basic phenomena of conditioning and learning can be demonstrated in the spinal segments of the mammalian nervous system. Attempts by several different investigators (25, 26, 47, 115, 198) to obtain conditioning in the spinal cord have met with failure. On the other hand, Shurrager and his colleagues have published a series of experiments (213–216) which they interpret in favor of spinal conditioning. These experiments, however, are open to criticism on at least two counts: *a*) what seems to be the CR may in fact be a UR (47); and *b*) what appears to be conditioning may be sensitization (114, 115). The question of spinal conditioning is therefore one that remains to be settled by future research (25, 26).

### *Subcortical Factors in Learning*

Relatively little has been done with lesions below the level of the cerebral cortex. Ghiselli & Brown (27, 77) made stereotaxic lesions in the thalami of a large number of rats, testing them thereafter on a variety of discriminative and maze learning tasks. Almost any thalamic injury outside the anterior nuclei significantly affected rate of learning, but on the whole the effects were not related to any set of nuclei. Allen (4, 5), working with the dog, found no change in a conditioned differential response to olfactory stimuli after ablations in the hippocampus, amygdaloid nuclei, pyriform areas, or in combinations of these areas.

Recent advances in our knowledge of the limbic system and its importance in emotion have turned attention to the role of this system in emotionally motivated learning (see Chapter LXIII by Brady in this volume). Septal lesions do not affect the learning of a classical CR to shock but do impair the retention of such a response learned before operation (21). However, learning of a conditioned avoidance response is more rapid in rats with septal lesions than in normal rats, and slower in rats with amygdaloid than in normal animals (116). On the other hand, retention of such a response is not impaired by amygdaloid ablation in cats (22). Much research of this sort is currently being reported, but it is not possible as yet to state accurately what the results imply about the role of the limbic system in conditioning and learning.

### *Conditioning in Decorticate Animals*

Pavlov's theory (181) originally explained conditioning in terms of cortical processes. However, many experiments in recent years have demonstrated that learning can take place in decorticate animals. If the learning task is one of simple classical conditioning, such animals show little or no impairment (44, 78, 189). However, if the task is one of instrumental learning, e.g. a conditioned avoidance response, animals have difficulty with it (44). Such responses can nevertheless be acquired, if the experimenter is careful to see that the animal does not become too 'emotional' (187), but the process is a slow one and under some circumstances will never be completed. Apparently then, the cortex is not necessary for classical conditioning (Type I), but it is important for avoidance conditioning (Type II) and more complex trial-and-error learning.

### *Maze Learning*

The maze is particularly suited to small animals such as rats, and for this reason Lashley used them extensively in his early studies of cortical factors in learning (125, 133). His general procedure was to make lesions of different sizes and in different locations in a large group of rats, some before learning the maze and some afterward so that he could study separately the effects of lesions on learning and retention. He also used mazes of varying difficulty. Upon completion of the behavioral work, he sacrificed his animals and reconstructed their lesions.

No particular locus of lesion proved to be more important than any other in impairing either learning or retention of the maze habit. Instead, the degree of impairment correlated well with the size of the lesion, irrespective of its locus. This general finding has been given the name 'mass action.' Moreover, the impairment depended on difficulty of the maze. With easy mazes, relatively large lesions were required to produce a given deficit; with difficult mazes, a relatively small lesion. Since maze tasks involve several different sensory and psychological capacities, and since a lesion made almost anywhere in the cortex is likely to impair one or more of these, it is to be expected that the larger the lesion, the greater the resulting deficit. Some consider this an adequate explanation of mass action (64). But Lashley has held (129) that in addition to specific functions of areas there are general, nonspecific functions of cortical tissue. Experimental difficulties, however, have so far blocked the resolution of this issue.

*Problem-Box Learning*

Several studies have utilized the so-called problem box—a compartment so arranged that the animal must perform some simple act either to escape or to secure a food reward. In the simplest case, a rat must learn to push two platforms in succession to obtain food (127). Learning such a simple habit, Lashley found, is unaffected by ablations of 50 per cent or more of the cortex; larger lesions than this may impair learning, but it matters little where they are placed. If the problem, however, requires much manipulative skill, such as pulling a string or turning a latch, it is more susceptible to impairment by cortical ablation, and there is a high correlation between the size of the lesion and the degree of impairment. This result is probably explained by the fact that rats subjected to operation are less resourceful and variable in their behavior and therefore have less chance of hitting on the correct solution to the problem.

Somewhat comparable experiments have been done with monkeys (104, 105). As one might expect, their ability to learn problems involving manipulative skill is impaired by lesions of the motor, premotor or both areas. However, it seems unlikely that the resulting impairment concerns learning ability or memory per se; rather it is probably the result of motor disability. In fact it is reasonable to believe that difficulties in problem-box learning by rats and monkeys are due to sensory-motor impairments and not to interference with learning or memory processes.

*Discriminative Learning*

Both Type I and Type II techniques have been widely employed in attempts to determine the effects of removal of some specified area of the cerebral cortex upon the learning or retention of a particular discrimination. It is most convenient to consider these studies by grouping them according to the sensory modality involved: vision, hearing and somesthesis. (For studies concerning only sensory capacity rather than learning and retention per se, see Chapter LX by Neff in this *Handbook*.)

VISUAL DISCRIMINATION. In general, simple visual learning and retention are unaffected by removal of the striate cortex. This is true of the conditioned eyewink in the dog (152), of leg flexion either to avoid shock (245) or to obtain food reward (246), and even of discrimination of a change in visual intensity (247).

When, however, an animal is required to make a choice between two stimuli, the results are somewhat different. While striate ablation usually has no effect on the learning of such a discrimination, when made after learning is complete it causes partial or complete loss of memory for the discrimination (117, 125, 128, 222). In the typical case of a rat, for example, the striate lesion causes complete amnesia for a discrimination of lights of different intensity, but the animal can relearn the habit in about the same number of trials as was required originally (125). This difference in the effects of striate lesions on learning and on retention is an important phenomenon that has not been satisfactorily explained (163, p. 470).

Animals need the striate cortex to perceive detail; without it they are completely unable, regardless of the amount of training, to discriminate forms like triangles, circles, squares, etc. (126). The discussion of this problem, therefore, belongs under the heading of visual capacities rather than learning. The possible role of the so-called association areas of the cerebral cortex in the learning and retention of visual form discriminations has been investigated. The prestriate areas lying adjacent to the striate cortex have often been regarded as the 'visual association areas.' Animal experiments, however, cast serious doubt on this supposition. Although results are not entirely consistent (1, 2), ablation experiments indicate little participation of these areas on the learning or retention of form (130, 203) or color discrimination (58)—at least when only these areas are removed. On the other hand, when relatively large lesions are made in the 'posterior association areas,' involving some combination of the prestriate, parietal and

temporal sectors, there is usually some deficit in an animal's ability to discriminate forms (2, 86, 203, 205, 242, 243).

In recent years, there has been considerable interest in the effect of ablations of the temporal (39, 40, 158–160, 188, 195, 204) and frontal (86, 167, 205, 242, 243) lobes on the learning and retention of form discriminations. Both lesions can produce impairments with, on the whole, injuries to the temporal pole being the more serious. On the other hand, depending on the type of discrimination required of an animal and on the size and locus of the lesion, there may be little or no impairment. Despite the great volume of research of this type, the results do not yet form a clear picture.

INTEROCULAR TRANSFER. In contrast, a definitive and interesting result is provided by some recent work on the interocular transfer of visual discrimination learning. Interocular transfer refers to the ability to recognize with one eye what has been seen and learned with the other. In this work, done with cats (171, 172, 227), the animals were first subjected to operations in which both the optic chiasma and the corpus callosum were sectioned in the midsagittal plane. This operation has the result of dissociating each eye from its opposite visual cortex and the two sides of the visual cortex from each other. After operation, one eye of the animal was blindfolded and training was carried out in the discrimination of such visual forms as a cross vs. a circle, horizontal stripes vs. vertical stripes, etc. After the animal had mastered the problem, the blindfold was transferred to the other eye. The result in every case was no retention; the animal showed no memory at all of what it had learned using the other eye. It was in fact possible to train the animal to learn conflicting habits with the two eyes with, say, a circle to the left eye positive and to the right eye negative.

Normally, of course, the mammalian retina projects to both visual cortices. These experiments demonstrate that, when this overlapping connection is eliminated, callosal association of the two cortices is essential to remembering 'with one eye what has been learned with the other.' This interesting result makes it clear that the memory of a visual discrimination habit is, under these circumstances, confined to one side of the cerebral cortex.

AUDITORY DISCRIMINATION. Studies of auditory discrimination have most often employed a conditioned avoidance technique (156, 186, 199), although there are some cases in which an animal has been required to give a conditioned differential response to stimuli (6, 239) or to locate the source of a sound in space (185, 206). The last named technique yields measures of auditory localization, whereas the former methods are better suited to intensity and frequency discriminations.

No matter what technique is employed, if an animal is trained in a discrimination and then is subjected to lesions of the auditory cortical areas, it usually exhibits some loss of memory for the auditory habit (59, 185, 186, 199, 206, 232). The amount of loss varies with the size and placement of the lesion and with the difficulty of the task. Unless the lesions are too large, however, the animal usually can be retrained to the preoperative level of performance (156).

An animal with a large ablation of auditory and associated cortex may, on the other hand, behave differently in two auditory tasks (66, p. 518). Thus, if two tones, A and B, are employed, cats will, after such an operation, relearn to respond appropriately to A as opposed to B (32). Relearning of the discrimination between the pattern of tones ABA and BAB, however, is not possible (51). This fact illustrates an idea often expressed, namely, that the cortex is required for discrimination learning when the task is 'complex' but not when it is 'simple.'

SOMESTHETIC DISCRIMINATION. The results obtained for somesthetic discriminations are generally comparable to those summarized above for auditory discriminations (208, 209, 239, 251–253). In this case, however, the relevant areas are somatic areas I and II and, more generally, the posterior parietal lobule. Sizable lesions anywhere in these areas usually cause temporary impairment of habits acquired prior to operation, but this typically can be effaced by some retraining. If, however, the discrimination is made relatively difficult, if the lesions include a large portion of both primary and associative areas, or if both of these conditions are present, the impairment may be severe and may not be effaced by any amount of training.

One of the relatively few studies on the effects of cortical injury in man on learning has been done with somesthetic discrimination (76). Individuals suffering unilateral penetrating injury of the cerebral hemispheres were trained in making a tactual discrimination of different forms. Normal individuals using either hand and individuals with brain injury using the hand on the same side as the lesion were

able to make progress in learning the discriminations. Individuals using the hand on the side opposite to their injuries were not, however, able to learn the discrimination. This failure to learn was not related to any sensory defect. Hence, we may conclude that at least some kinds of learning depend on the hemisphere receiving the main sensory projections of the somesthetic system.

This finding is related to a recent study of the function of the corpus callosum in the contralateral transfer of a somesthetic discrimination in the cat (228). Cats were trained to use one paw to push the correct one of two levers on the basis of tactual form, softness or roughness (three different habits). After the discrimination had been thoroughly learned, the cats were required to make the same discrimination with the forepaw not used in the original training. Normal animals did this with relatively little additional training, but cats in which the corpus callosum had been sectioned prior to the experiment took as many trials to learn it as they had in learning the original discrimination. Hence, the corpus callosum seems to be essential to the transfer of somesthetic habits from one side to the other just as it is in the experiments cited above on interocular transfer.

DELAYED REACTION. As described earlier only a slight change in procedure is necessary to convert the conventional discrimination problem into a test of delayed reaction (or response). In this test, the animal is shown the correct stimulus, then required to wait for a few seconds or minutes before being allowed to make its discrimination between two stimuli. As first employed by Jacobsen (106), it was regarded as a test of immediate memory. The factor, however, that often determines success or failure in the test is whether or not the animal pays attention to the correct stimulus when it is first shown.

Jacobsen first demonstrated that monkeys with frontal lesions have difficulty in the delayed reaction test (106). This fact has been confirmed many times in subsequent studies (16, 65, 86, 155), but it is not a universal finding for such monkeys sometimes can succeed in the test (33, 167). Moreover, by making such minor changes in the procedure that the animal's chances of attending to the presentation of the correct stimulus are increased, substantially all these animals can succeed in passing the test (63, 151, 223). This fact indicates that the impairment is more one of attention than of immediate memory (85, 87). There is some evidence that an area lying in the dorsolateral frontal region anterior to the precentral motor cortex is especially important in delayed response performance (194, 197). There is also evidence that areas outside the frontal lobe are not important (107, 154), although a deficit in delayed reaction is reported occasionally in animals having posterior lesions (130).

Closely related in principle to the delayed reaction are tests of double alternation or delayed alternation (144, 164). In double alternation tests, the animals must respond in a pattern of RRLLRRLL. In delayed alternation, it must respond RLRL after a delay between each response. In all such tests, the important element is that the animal must remember what it has previously done or experienced in order to know what to do next. In all such tests, too, frontal ablations are usually followed by substantial impairment (134, 144, 164, 196).

CONDITIONED INHIBITION. Konorski has recently reported (28, 122) a series of experiments on the role of the frontal lobes in conditioned inhibition. Dogs and cats were taught a conditioned discrimination by setting up an excitatory reflex to one stimulus and an inhibitory reflex to another. Following this training, ablations were made in frontal areas and in parietal areas, usually in different animals but sometimes in the same animal. The general result of frontal ablation was to impair inhibitory reflexes without affecting excitatory reflexes. That is to say, frontal animals made correct responses to positive stimuli but also made these responses, which they had been trained not to make, to negative stimuli. Parietal lesions, however, had no significant effect on the retention of conditioned inhibitory reflexes. These conclusions apply about equally well to salivary responses (classical or Type I conditioning) and to motor foreleg flexion (Type II conditioning).

ANTICIPATION AND PERSEVERATION. Learning tasks can be so designed that they involve a series of responses leading up to a goal. A maze constitutes such a task, but so also do some problem boxes in which the animal is required to do two or three things in a particular order. If the animal is unable to perform the task correctly, two kinds of mistakes are fairly common: one is to anticipate a correct response, making it too soon in the series of the response; the other is to perseverate, making the same response two or three times in succession.

Disorders of serial learning appear with almost any large lesion of the cerebral cortex, but they are especially prominent after frontal ablations. Thus

rats (34, 57, 150, 231) and monkeys (106) with such lesions tend to make more perseverative errors and anticipatory errors than normal animals or animals with more posterior lesions. This impairment is probably closely related to the deficit seen in the delayed reaction.

*Summary*

Since psychologists have not seen fit to agree on any single set of procedures to be employed in studies of conditioning and learning, many different learning tasks—more than there is room to describe here—have been devised for the study of the effects of ablations. Furthermore, different experimenters often do not make the same lesions even when they intend to do so. As a result, ablations may produce impairment on some tasks and not on others, and experiments do not always agree with each other because of minor differences in procedure.

Despite these and related problems, certain facts seem clear. When the habit requires a sensory capacity (e.g. form vision) abolished by the ablation, no amount of retraining ever effaces the deficit produced, as might be expected. On the whole, however, cortical ablations have little or no effect on classical CR's; animals learn these just as easily after injury as before and retain them after lesions are made. But if differential CR's are called for (or if the learning task involves instrumental responses), retention is often impaired; thus, typically, removal of the primary sensory area relevant to the habit causes a partial or complete memory loss, but the animal relearns in a reasonable number of trials. If a number of sensory modalities are concerned, as in maze learning, then one sees a mass-action effect—a correlation between amount of deficit and size of the cortical lesion. And, finally, lesions that include all primary and association areas of one modality may cause considerable, lasting impairment.

The posterior association areas lying in the parietal-occipital-temporal sector are proving to have considerable importance, particularly in discrimination learning. Certain parts of the temporal pole seem especially implicated. The frontal areas are clearly involved in learning where the ordering of responses in time is a critical feature. When learning involves the cortex of one side only, the corpus callosum plainly participates in its transfer to the opposite side, at least for some habits.

EEG CORRELATES

Promptly after Berger's rediscovery of the brain waves, serious attempts were made to put these electrical events to work in uncovering the neural events of learning and conditioning. In the following description of these efforts it must be taken for granted that the reader is familiar with certain general propositions about brain waves, neurophysiology and neuroanatomy. The reader may wish to consult Chapter XI by Walter of this *Handbook* in which autogenous brain waves are discussed.

The search for electrical brain events reliably related to learning began with the discovery that exposing the eyes to light leads to the disappearance of alpha waves. It was soon found (54, 143) that simply pairing a sound (CS) with the light (US) led rather promptly to disappearance of the alpha waves in response to the sound alone. Thus there started some 20 years ago a new and potentially fruitful era of research that is currently in full swing.

*The Alpha Block CR*

The cortex of most animals generates a more or less continuous series of waves in the region of 5 to 20 per sec. The exact frequency range varies with the species studied, and for man the figure 9 to 11 is ordinarily given as normal. For convenience these all can be called alpha waves. Experiments in which their disappearance is conditioned to a stimulus typically proceed as follows.

The scalp EEG is recorded from the subject at rest and in the dark. From time to time a light is turned on and off; the alpha waves disappear as long as illumination continues. From time to time also a sound is turned on; at first this stimulus, like the visual stimulus, temporarily blocks alpha activity, but eventually it does not do so, an example of habituation (70, p. 16; 165). Finally the stimuli are paired, with sound (CS) preceding light (US) by a brief interval. Shortly thereafter the alpha rhythm disappears as soon as the sound comes on and the alpha block CR has been established.

Where no motor response is employed, the term sensory-sensory conditioning is applied to these EEG studies. The blocked ('desynchronized,' 'arrested,' flattened') EEG response is, in addition, a common event in Type I and Type II conditioning procedures.

Morrell & Jasper (165) contribute a recent example of the so-called sensory-sensory experiment. Tones paired with light produced conditioned alpha block

in an average of 11.1 trials in 8 monkeys with implanted cortical electrodes. When instead of sound a second visual stimulus or mild shocks to the skin were used as CS, averages of 13.2 and 9.5 trials, respectively, were required. A remarkable increase in trials is required when epileptogenic lesions (produced by alumina cream) exist in the cortical projection area specific for the CS or in the amygdala (166).

In studies on man, Motokawa (168) paired sound (CS) with light (US), recording, in addition to the multiple scalp EEG, the galvanic skin response (GSR). Both the alpha block and the GSR became conditioned to the sound alone. This finding, besides portraying the EEG details of a typical 'sensory-sensory' procedure, shows that the alpha block CR may be highly correlated with an autonomic CR. These observations have been confirmed (103), and similar results were found in a Type I situation where salivation instead of GSR was conditioned to a sound (102).

The alpha block CR may be preceded by a period of enhanced alpha amplitude if the interval between application of CS and US is sufficiently prolonged (101). On the other hand, Motokawa & Huzimori (169) have shown that more than one alpha block CR may occur during the conditioning procedure. They used a bell (CS), and a shock to the foot (US) in man, recording both the GSR and EEG. If the bell was sounded for some 10 sec. before application of the US, alpha block occurred both at the onset of the CS and again just prior to its termination. A GSR response coincided in time with each alpha block when conditioning was well established. Both periods of alpha block seem to meet the criteria for CR's (102, p. 352).

Kogan (118), finally, has used microelectrodes implanted in cats to study the cortical events occurring during the conditioning of a motor response to an acoustic stimulus. Alpha block seems to be a constant feature of the process, occurring first in the auditory area and spreading later to the motor region. In addition, beta waves and 'special forms of electrical activity' (not further defined in the brief English report seen) appear. In the early stages of conditioning, changes are prominent in cortical layers III and IV, but later a shift to 'the deeper layers' is noted. According to this report, very large oscillations of potential appear in the auditory cortex when a differential CR is set up with auditory stimuli. The use of microelectrodes is just beginning in non-Russian hands, but it has already revealed some valuable information (29, 202).

The alpha-block CR obeys, more or less, the general rules established for conventional CR's. It appears only after a number of pairings of CS and US, and some stimuli are more effective than others (165). Furthermore, when only one of two different sounds is reinforced, the reinforced sound alone evokes the CR, an example of differential conditioning (165, 207). Finally, if the CS is not reinforced, the CR disappears; this is the phenomenon of extinction.

Some attention has been given to the cortical regions blocked in the response. Prior to its habituation, the CS preferentially blocks the parietal region (165) or the brain in general (70), but after establishment of the CR it specifically blocks the occipital region (165) or the cortical region to which the sensory system of the US projects (70, p. 16). If the CS is applied to one side of the body, the conditioned EEG response may even be limited to the contralateral cortex (70).

The reliability with which alpha block appears in conditioning experiments leaves much to be desired. Certainly it does not invariably occur and in one lengthy and important study, for example, 60 per cent success is reported in a large group of human subjects (70). Consequently the alpha block CR may be of limited usefulness in understanding the basic neural events in conditioning. The phenomenon is related to action of the reticular formation discussed in this *Handbook* in Chapter LII by French and elsewhere (3, 69, 248–250); it appears when the animal is merely alerted as well as during the learning process. Nevertheless, as we have seen, the alpha block CR satisfies many of the criteria for a cortical event that accompanies learning.

### *Cortical Evoked Potentials*

In addition to its regular rhythmical activity, the cortex generates brief electrical waves corresponding to the arrival within it of impulses from the various sense organs. These so-called evoked responses follow sound, light, touch and similar stimuli. Their latency, magnitude and duration have been examined during the conditioning process.

In an important variation of the sensory-sensory conditioning procedure, for example, a flashing light is substituted for the continuous one. Not only does the regular cortical rhythm disappear, but evoked cortical waves harmonically related to the frequency of the flashing light are recorded ('photic driving'). If a sound (CS) is now made to precede the flashing light (US), the sound alone eventually produces an EEG response remarkably similar to the characteristic

'photic driving' pattern. Analogous results are reported in Type I learning as well as in sensory-sensory learning (70, 210, 248).

One of the earliest studies of cortical evoked potentials as influenced by learning is the work of Livanov & Poliakov (140) on the rabbit. Shocks to the leg (US), paired with light flashes, led in time to leg flexion (CR) upon presentation of the light alone (CS). Both light and shock occurred at 3 per sec. During the learning process a 3 per sec. rhythm appeared first in 'certain' cortical regions, later in the whole of it; when the CR was fully developed 3 per sec. rhythms of large amplitude tended to be present during the CS and to be absent at other times. However, every motor response, whether spontaneous or provoked by painful or other stimuli, was now accompanied by the 3 per sec. rhythm. The authors suggest from this that "the process of formation of the conditioned reflex defense reaction in response to the rhythmic stimulus is developed on the basis of a system of rhythms reflecting periodical changes in the excitability of the motor centers of the cortex" (see also 80, 165, 190).

The brain wave CR pattern evoked by the CS approximates the frequency of the photic stimulus US better and better as conditioning proceeds, and the CR appears progressively earlier in time (165). It is limited to the occipital leads, is unstable as compared to the alpha block CR, and it quickly extinguishes (165). This CR appears not only at the cortical level but also in thalamic and mesencephalic regions where it is reported to be large and stable (250).

The evoked response to sound also undergoes interesting changes. Its magnitude has been shown to vary somewhat from one stimulus to the next in the untrained animal, but a Type I conditioning procedure stabilizes such responses at large amplitude in the auditory region (67, 110). Evoked responses also appear in cortical areas not previously involved and the complexity of all of them increases, with those features that follow the click by 30 to 100 msec. ('secondary' responses) being particularly influenced.

Artemyev & Bezladnova (10) undertook in cats "to follow the dynamic changes in the nervous processes of the cerebral hemispheres arising out of the development of conditioned reflex links." A 1 kc tone, 60 db above the human threshold and lasting 1.3 sec. constituted the CS, with shocks to the hind leg as the US. The EEG onset response to the tone was recorded on a cathode ray oscillograph. Electromyograms of the leg muscle showed that 10 of 12 cats developed the CR ('defensive conditioned reflexes'). In all animals a positive correlation is reported between the CR and the occurrence of EEG change in the auditory area as follows. "Where the percentage of occurrence of the electrical reaction in the cerebral cortex is low, the conditioned reflex is absent," and "in the course of forming the conditioned reflex in the auditory projection area with sound stimuli, the primary electrical reaction occurs in a markedly greater number of cases than before and at the beginning of the combinations." Fluctuation in magnitude of the EEG response was seen during the conditioning process and during extinction. The response disappeared in sleep and with simultaneous "strong stimulation of other analyzer systems." The findings are discussed as follows: "If the animal is passive to the stimulus the level of excitability of the neurons of the cortex is lowered and the primary electrical reaction is decreased in amplitude and disappears. When the ineffective stimulus is linked with another which is biologically important to the animals, the excitability of the nervous elements increases, of which we can judge by the more frequent occurrence of the primary electrical reaction."

Confirmation of these observations has in the main been reported by others (e.g. 67, 110). Since, however, similar results have also been obtained at the level of the cochlear nucleus (67, 90, 91, 110, 142), the changes seen at the auditory cortex may merely reflect events that occur at subcortical levels.

### *New Electrical Waves*

Among the least understood of the central correlates of the CR are the 'new potentials' that have been reported to be associated with the conditioning process. Many published records show high- or low-frequency events not characteristic of the normal record; these either appear during the alpha block or, when alpha is present, constitute distortions of the base line. These new events bear no relation to the stimulus frequency as is true of the evoked potentials just discussed.

In man they may be beta (20 to 30 per sec.), kappa (10 per sec.) (9), or theta (5 per sec.) waves. Motokawa & Huzimori (169), Motokawa (168) and Iwama (101) consider the high amplitude waves at 3 to 5 per sec. ('excitation potentials') to indicate increased activity of the area in which they appear, this presumably being a necessary precursor of the cortical events in conditioning. Popov (190), however, has shown the occurrence of such waves in the parietal

cortex of rabbit to be the major electrical event paralleling the development of Type I conditioning to a sound CS followed by shocks (US) to the paw. If the shock to the paw is very weak, on the other hand, the sound CS produces alpha block that unmasks bursts of high frequency waves, but no 3 to 5 per sec. waves whatever appear. This report raises the important but unsolved question of what systematic EEG differences, if any, are associated with variation in strength of both CS and US. Popov & Popov have further been concerned with long-lasting cyclical alterations of alpha amplitude that accompany light flash CS; the original papers should be consulted for the relation of these to visual afterimages and regarding their conditioning by sounds (191–193).

*Subcortical Structures*

Much recent experimentation has dealt with electrical activity in subcortical structures during Type I learning. Behind this work lie the three new concepts about the nervous system that render obsolete so much of the neurophysiology of 5 or 10 years ago. These are *a*) the demonstration in unanesthetized animals of the widespread influence of the reticular formation upon the organizing and integrating functions of the brain, *b*) the possibility that the descending sensory pathways constitute 'feed-back' loops for control of afferent input to the brain, and *c*) the concept that limbic system structures are intimately concerned with emotional behavior and thus with any learned activity that has an emotional component. The reader will find these ideas discussed at length elsewhere in this volume. Our interest is in those experiments which have been done to relate them specifically to the learning situation.

It is clear that a CS (e.g. auditory clicks) not only evokes the expected responses throughout the appropriate sensory system but in addition activates parts of the brain to which anatomical projections from that modality have not been described or are poorly understood (e.g. limbic system, reticular formation). At a given recording site, the responses vary widely in amplitude, latency and duration, but these features have not yet been properly analyzed. Thus far, the only reasonably consistent finding is that some electrical response to the CS tends to be large and stable in the conditioned animal, while being small, labile and recordable at fewer brain locations in the unconditioned or extinguished animal. As in the case of cortical electrical correlates, however, agreement has not been reached as to which subcortical events are invariably related to learning.

Important information on events in the lower nuclei of classical afferent pathways comes mainly from the auditory system of cats. Hernández-Peón and associates (90) studied the response of the cochlear nucleus in Type I learning to tonal stimulation (CS) paired with shock (US) to the hind leg. The cochlear nucleus response, having diminished in size during habituation of the animal to the apparatus, attained large size and increased duration when the conditioned leg withdrawal was fully developed. Similar results have been reported in cats that received shocks irregularly when click stimuli were being presented (67); correlated with the behavioral response developed to clicks, the evoked response in the cochlear nucleus and medial geniculate (and auditory cortex as well) became large and regular in comparison with responses in the habituated and extinguished state (see also 30, 31, 91, 110).

A small amount of information is available about the activities of the limbic system in conditioning. Waves of 3 to 5 per sec. from a presumed caudal hippocampal location have been reported to fill the CS-US interval in a Type I situation; but such waves were absent from septal and other hippocampal locations (149). Evoked responses appear and become stable in the hippocampus and amygdala as well as in the caudate nucleus when a sound US is employed in Type I conditioning (67). The amygdala of the cat seems unique among limbic structures in that 40 to 45 per sec. waves of high amplitude appear in it during conditioning of a shock to sound (135); these diminish or disappear with extinction and can be re-established by repetition of the conditioning procedure.

As for the reticular formation, some remarkable electrical events within it appear to be related to the learning process (250). Cats were prepared with electrodes in the cortex, reticular formation, and ventral anterior and center median nuclei of the thalamus. A tone (CS) was presented for 5 to 10 sec., followed shortly after its onset by a brief train of light flashes at 5 per sec. (US). After many pairings, the tone alone produced both the alpha block CR and new waves in the cortical leads. In addition, a 5 per sec. rhythm appeared in the subcortical locations which, at the reticular formation leads in particular, developed promptly upon the tone-onset and persisted long after the tone was turned off. After very many pairings, the 5 per sec. rhythm might last for more than a minute when the animal

was located in the experimental room, but they failed to appear if the recording was done elsewhere in the laboratory. The authors were impressed by the durability and persistence of the subcortical rhythms as contrasted to the transitory characteristics of the cortical ones.

*Summary*

Certain generalizations about learning derived from the EEG responses can be made with the reservation that they do not always agree with all the data. At the cortex the CS comes to block alpha waves in a new way that parallels the development of the CR in time. Besides this, the CS can arouse new cortical waves whose existence seems to depend upon the learning process. And finally, the cortical responses evoked by the CS can be larger, more complex and more stable during acquisition and retention than they are during habituation and extinction.

But entirely similar electrical changes are also taking place in many other brain locations. Before conditioning, what is to become the CS causes a variable evoked response in the afferent sensory tracts and in limbic structures; these, like their cortical counterparts, become larger, more complex and more stable in learning. The new cortical waves are matched by novel events in limbic and reticular structures that are exactly similar in principle and perhaps even in kind; such waves in the reticular substance may actually be far less fickle and evanescent than the cortical ones. And, finally, the cortical alpha block probably reflects mainly the action of the reticular formation. Thus limbic, reticular and cortical structures are all involved in learning, if the EEG results are to be believed. How one can objectively determine from this evidence alone that one part of the brain is more involved in learning than another is difficult to see. Nor is it possible at the present time to do more than guess at how the three major systems—cortex, reticular formation and limbic system—interact with one another. There seems to be little question that they do so, and some interesting fundamental facts will inevitably emerge from experiments directed at this question.

The psychologically oriented reader will want to know how well the EEG findings, such as they are, correlate with the types of learning recognized in his system. If he favors the Pavlovian analysis of conditioning he will find Gastaut's summaries (69, 70) and that of Buser & Roger (31) informative. In terms of the analysis of learning presented earlier in this chapter we can say the following. Type I, Type II and perceptual learning are not yet distinguishable on the basis of their EEG characteristics. Acquisition is accompanied by widespread electrical events, but no single set of them is crucial. A clear case can be made for the involvement of the reticular formation in habituation and extinction; and insofar as attentive functions play a part in learning, the reticular formation is also unquestionably involved. The EEG responses often correlate poorly with the behavioral responses, that is to say, they are not invariably present when the CR appears, nor are they always absent when it does not. A beginning has been made in the study of differential conditioning and of the emotional versus the operant continuum. Taking it all together, EEG correlates have been found for many behavioral manifestations in learning and it is safe to predict that many more will be uncovered when precise modern behavioral control is combined with the electrophysiological method in the study of animal preparations.

It must be confessed that, from the physiological point of view, the data available are still scattered, fragmentary and incomplete. The important question of localization of events in different cortical areas, for instance, has been addressed in very few studies, and so long as scalp electrodes are employed, definitive answers probably cannot be expected. This point may be settled by the implanted microelectrodes just coming into use.

## BRAIN STIMULATION

Electrical stimulation of the brain of the unanesthetized animal combined with a simultaneous measurement of behavior is a technique being increasingly employed. In the area of our concerns the objectives are to produce or modify learned behavior by activating the brain in some artificial order or unnatural degree. Such studies, as we will see, have already developed some interesting information.

*Brain Shocks 'Produce' Behavior*

While shocks delivered to many brain locations have no effect whatever upon behavior, at other locations the same shock schedule may produce dramatic events indeed. Animals that are awake can be put to sleep and vice versa; peaceful animals can be made to attack viciously, quiet ones become active, and autonomic responses like salivation and defecation are

commonly induced (94, 95, 146–148). Presumably the locations stimulated represent places where something important for the behavior observed is centered. Through such experimentation, in part, the limbic system has become strongly implicated in emotional behavior (see Chapter LXIII by Brady in this volume) and the reticular formation in attentive functions. We shall restrict ourselves here to the experiments relating electrical stimulation specifically to learning.

*Brain Shocks as CS and US*

In Type I learning, as we have seen, two stimuli appear in the animal's environment. Commonly the US is a shock that activates pain receptors of the skin while the CS is a tone or light that activates the ear or eye. The question of whether shock to the brain can replace either US or CS or both has prompted a number of studies. There has been considerable controversy about this problem and particularly about the question of whether the shocks simply activate afferent fibers where they are collected together in the brain instead of where they are dispersed in the periphery. This point seems to have been resolved, in some cases at least.

Doty *et al.* (52) in cats paired shocks (CS) to the cortex with shocks (US) to the paw. All their animals learned within 400 trials to lift the paw to escape the leg shock when the only signal of its imminence was the cortical shock. It made little difference whether the CS was applied to marginal, postlateral, middle suprasylvian, or middle or posterior ectosylvian gyri; even a point on the frontal cortex was effective. A very careful series of control studies shows that neither receptors in the membranes covering the brain nor other sensory stimulation of the head constituted the CS. This report summarizes previous experiments on the problem and fully discusses the value of such studies.

Delgado *et al.* (48), following on the pioneering efforts of Gantt and colleagues (24, 68), have used shocks applied to thalamic, mesencephalic and limbic structures of cats as US. Such shocks produce violent 'fear-like' responses which the animals presumably do not enjoy. They used a Type II avoidance technique with flickering light (or a 2000 cps tone) as the CS; the brain shock (US) could be prevented if, within 5 sec. after the CS appeared, the animals rotated a wheel. After 16 to 92 pairings, each of four cats regularly turned the wheel and thus avoided the brain shock. Control experiments include the demonstration that, before training, the CS alone did not cause wheel turnings. The possibility that collected afferent tracts or normal pain or other end organs of the head were stimulated was not excluded, although such explanations seem unlikely. The authors demonstrated, in addition, the important fact that shocks to the motor cortex failed to serve as US in the animals in which subcortical shocks succeeded, and they describe three other situations in which cortical shocks proved to be effective unconditioned stimuli. In one of these learning was actually produced by pairing cortical (CS) with subcortical (US) shocks, thus bypassing all normal sensory input channels. A recent report that a monkey will operate a lever to escape a brain shock confirms one of the findings of this study (138).

Much experimentation along these general lines is to be found in the Russian and eastern European literature. Kupalov (124), Giurgea (79–81; see also 124) and Rusinov (207, 210), for instance, report use of either shocks or direct currents to affect the cortex, and Grastyan *et al.* (82) stimulated limbic (hippocampal) structures. Giurgea produced leg flexion CR's by pairing occipital cortex shocks (CS) with shocks to the motor cortex (US) in the dog. No EEG changes accompany the conditioning process, and lesions of the reticular formation and corpus callosum do not influence it.

A special word is in order about the experiments of Rusinov. These employ weak direct currents applied to cortex, hypothalamus and other brain regions. A key principle in some Russian circles is the idea of 'dominants' enunciated by Ouktomski (136, 190) according to which the US makes its cortical area hyperexcitable, thus producing the 'focus' to which the effects of the CS are attracted in the conditioning process. Attempts to create or simulate such 'dominants' by direct currents and drugs are a feature of many experimental designs.

These experiments show that normal sensory events are not invariably required for learning, however useful they may ordinarily be in the process. The execution of the peripheral motor response is not necessary either, for if the procedure that produces conditioned leg flexion in a normal dog is applied to a dog which cannot move the limb because its motor nerves are destroyed, the conditioned leg flexion is nevertheless found after the nerve regenerates (12, 137). In a similar way salivation can be prevented by drugs while conditioning is carried out and yet appear later when, without drugs, the CS is applied (43). One can therefore conclude that, in some cases at

least, neither the peripheral sensory nor the peripheral motor response is required for conditioning.

*Self-Stimulation*

An entirely new line of brain stimulation experiments began with the discovery (179) that under proper conditions animals will work hard and consistently to shock themselves if given the opportunity to do so. In these studies a switch is put within reach of an animal; when the switch is closed a train of shocks is delivered through electrodes implanted into certain regions of its brain. Monkeys, rats and cats in this situation very soon spend most of their time closing the switch. It is clear that the brain shock serves to reinforce the behavior, surprising as this may seem.

The learning of this behavior may be extremely rapid, for a very few brain shocks often suffice to make the response rate reach the maximum which the animal ever displays. Once learned, the behavior is stable and obeys many of the standard laws (219). There are some indications that extinction, however, is very quick, at least in the early stages of learning. Preliminary reports of competition between this behavior and other activities including learning have appeared (42, 177, 178).

It was found very early that shocks to all brain locations are not equally reinforcing and that, in fact, the animal will not close the switch a second time for shocks in some locations. Animals stimulate themselves actively when the electrodes are in the limbic system, or in mid-line structures in the hypothalamus and rostral midbrain (176). Negative locations are closely adjacent.

It is still too early to assess the full significance of these experiments. There is much interest at the speculative level (which perhaps the reader shares) regarding what the animal 'feels' during self-stimulation; perhaps direct tests will settle this point in man. More objectively, the technique provides a clean new method for classifying brain nuclei and tracts in terms of whether shocks to them are rewarding (i.e. reinforce the behavior), punishing (i.e. depress it) or indifferent. The preliminary brain classification presently available, when compared with the ones derived from anatomical and physiological techniques, has already revealed that the punishing and rewarding points tend to lie in structures implicated in the motivational, emotional and attentive mechanisms in learning. This growing body of information must therefore be watched with much interest.

*Brain Shocks Influence Learned Behavior*

When shocks are applied to the unanesthetized human brain exposed at operation the patient may recount 'memories,' some of which could have been deliberately learned. Presumably a particular set of neural connections has been activated by the punctuate stimulation applied (184). The barest beginning has been made in attempts to apply this general idea to animal experimentation and to produce changes in acquisition and retention thereby. Shocks applied to the cortex of rats improve learning of a maze and accelerate formation of visual discrimination, but these effects are barely significant statistically (72, 73). Thalamic shocks applied to cats pressing a bar for a food reward reduce the rate and increase the irregularity of the response (37). Stimulation of the caudate nucleus abolishes an avoidance response in dogs, but shocks to the pulvinar fail to do so until they are made very strong (36). Clearly the information on this point does not warrant any generalizations at this time.

*Electroconvulsive Seizures*

The clinical observation that human beings undergoing convulsive therapy tend both to forget recent events and to undergo changes in their emotional behavior has led to a number of experimental attempts to define the neural mechanisms involved. Animals, like people, quickly recover from the violent convulsions and unconsciousness produced by electrical currents passing through the head, and they appear grossly to be normal some minutes later. In many respects they may well be, but careful testing has already revealed that electroconvulsive seizures (ECS) have certain specific effects on learning.

ECS, for example, impairs acquisition. Duncan (53) demonstrated this by training rats in an avoidance task, subjecting some of them to ECS promptly after each trial while delaying it for others. The animals receiving ECS 20 sec. after each trial acquired the response very poorly, while those for which ECS was delayed 1 hr. were indistinguishable from the controls. The intermediate delays (40 and 80 sec., 4 and 15 min.) yielded the expected intermediate degrees of learning. Entirely similar results have been reported for hamsters in a maze test (75) and for rats in a discrimination problem (234). The fact that heat narcosis at various times after the final learning trial affects learning in goldfish in a manner comparable to that of ECS in rats suggests that acquisition takes time in all animal forms (35).

ECS may also have differential effects upon two behaviors—it may leave one kind entirely unaffected while attenuating or even abolishing another (20; 71, p. 370; 89). For example, a thirsty rat trained to press a lever for drops of water will do so just as well after ECS as before. If, however, it has also been trained to 'expect' a painful shock following an auditory stimulus, the animal fails after ECS to display any signs of this conditioned emotional response (20; see Chapter LXIII by Brady in this volume). The conditioned emotional response (CER), consisting of immobility and autonomic events like piloerection and defecation, disappears completely for many days, returning, however, without further training in a matter of weeks.

These experiments specify two novel aspects of the central correlates of learning. In the first place, they are not instantly established; a period of time follows the termination of the actual conditioning situation during which the central changes 'gel,' so to speak, and the temporary connections become stabilized. In the second place, central connections behave differently when subjected to disrupting influences; the CER, which by most criteria is an extremely stable response, vanishes with ECS while the operant CR remains apparently untouched. Whether this means that the correlates for CER and CR are different in place or in kind remains to be seen, but a real difference between them has been defined by an elegantly simple experiment.

*Summary*

Psychologists recognize many temporal variables in learning and have extensively studied the effects of reward and punishment upon it. The brain stimulation experiments, taken as a whole, provide some glimmerings of what central events underlie these phenomena. The process of acquisition, it appears, goes on for a considerable time after the actual training is over. Furthermore, the events related to 'memory' can be greatly disturbed, with certain types of learning suffering far more than others in this regard. As for rewards and punishments, the possibility of specific centers for each of these seems open to experimental attack through the self-stimulation technique.

Besides this, the experiments have made it clear that the locus of the temporary connections in learning lies in the brain. This probably surprises no one, but there is certainly no harm in having the fact experimentally established. The important point is, however, that the places where and the processes wherein CS and US become connected can now be explored, if desired, without interference from neural activity in those parts of the system that merely conduct information from and to the body surface. There is, finally, good reason to believe from self-stimulation experiments and similar evidence that the central regions related to CS and US have significantly different properties.

## PSYCHOPHARMACOLOGY

Until recently the use of drugs as tools for dissecting the learning process has been somewhat unrewarding. Two bibliographies assembling many hundreds of publications attest to the devotion with which investigators have attempted to show specific effects of such agents upon acquisition, retention and extinction (8, 18). The failure as yet of any system to emerge from all this effort may be hard to understand at first glance, for it has long been obvious that chemical substances in the blood stream may have really profound effects upon learning. For example, relatively small amounts of anesthetics unfailingly reduce animals and men to a state where no learning whatever is possible. One might naively expect that between the stages of complete anesthesia and none at all a level would be reached where the learning process was, say, only half impaired. Such a stage has, however, never been defined. Similarly, no one questions that a child with thyroid gland deficiency learns poorly and that specific replacement therapy goes far toward restoring him to normal; the explanation for this is, however, still a mystery. Discussions showing the inconclusiveness of studies with hormones (71, p. 386) and other biochemical factors (163, p. 532) in learning are available; Wikler's summary (244) should prove especially useful.

Within the last few years research using drugs in behavioral studies has accelerated remarkably, due in part at least to the advent of new synthetic and natural substances having powerful effects upon behavior (e.g. 'tranquilizers'). Recent symposia (50, 62, 109) summarize the present status of the new discipline of psychopharmacology that is in the process of evolution. In one of these (50) six papers deal specifically with drugs and learning. Sidman (218), for example, fully discusses the interaction of behavioral and drug variables, and demonstrates with numerous examples how a given drug may be assayed for its action upon many different learning situations in the same animal. While no general principles of the action of drugs in learning can yet be stated with certainty, the results

available show some of the ways in which drugs may eventually prove of great analytic value.

*a*) A given drug (in this case, reserpine) may have no effect upon acquisition of a CER (229) but may attenuate its expression remarkably.

*b*) When employed in trained rats displaying three different learned responses, a drug (again reserpine) may severely depress two of these without affecting the third, or interfere with one of them and enhance another even though both presumably create 'anxiety' in the animal (218). Such specific differential effects upon behavior mean, we must presume, differential influence upon the underlying neural events.

*c*) We have already seen that animals will operate a switch in order to procure shocks in the brain, and that the highest response rates are attained with shocks delivered to the limbic and hypothalamic structures implicated in emotional behavior (19; see Chapter LXIII by Brady in this volume). If an animal behaving in this manner is given a tranquilizer (reserpine or chlorpromazine), a sharp decline in rate of self-stimulation ensues, while with pentobarbital no drop is seen (178). The tranquilizer would appear somehow to reduce the reward value of the brain shocks; how, if at all, this is related to the processes of learning is an interesting matter for speculation and further study.

*d*) Drugs, finally, act differently upon the neural processes in discrimination. Blough (15) has shown that pigeons are better able to make a certain visual discrimination under the influence of LSD and less able under chlorpromazine, although in neither case is their ability to peck at the visual targets employed different from the control. It is not possible as yet to state where in the nervous system the effects required to explain these results could be exerted.

### *Summary*

Any discussion relating the budding field of psychopharmacology to problems of learning must necessarily be inconclusive at the present time, for until recently the available data have settled few, if any, questions. However, much activity along new and promising lines is now in progress.

## NEUROPHYSIOLOGICAL THEORIES

We propose in this section and the next to state where we stand in our understanding of the learning process. In the preceding sections the facts thus far wrested from nature by much hard work—both intellectual and experimental—have been assembled. Can anything be done with them toward synthesizing a concept of the essential features of the process? We will first outline the ideas others have had and then proceed to some of our own.

### *Change in Central Synapses*

The inference that the learning process is to be explained by a specific change in central synapses has had a particular appeal. According to this idea something called 'synaptic resistance' is lowered, or, put another way, the efficiency of synaptic action is somehow increased during learning at those places where the temporary connections are made and this increase may become more or less permanent. There are two main classes of such ideas; one holds that the changes are chiefly anatomical, the other that they are primarily biochemical.

ANATOMICAL THEORIES. The anatomical explanations are numerous. Some of these stem from the observations upon embryos that led Kappers to offer his theory of neurobiotaxis as an explanation of the means whereby neurons come to make their proper connections in the first place (111). He supposes electrical or metabolic gradients, or both, to be developed in tissues and to attract growing nerve fibers. In learning, similarly, foci of activity are supposed to be created in certain neurons by the stimuli, these foci attracting neurons or parts of neurons. A formal statement of this idea has been given by Holt (99).

Recent discoveries about the anatomy and physiology of synapses have led to more specific variants of the neurobiotaxis theme. Thus Hebb (88) visualizes the axon terminals of one presynaptic element to multiply in number during stimulation, an anatomical change that would enable the element to increase its contribution to the depolarization of the postsynaptic neuron. Konorski (120, p. 86) considers "formation and multiplication of new synaptic junctions between the axon terminals of one nerve cell and the soma (i.e., the body and dendrites) of the other" to be the responsible factor in the elaboration of conditioned reflexes, with "fading or atrophy of synaptic connections" occurring when the US is withheld. Eccles (56) holds that axon terminals swell in size during activity, thus increasing their area of contact with and capacity to influence the postsynaptic neuron. Finally, the neurohistologist Sarkisov (212) reports seeing much variation in the

structure of cortical synapses and suggests that morphological changes in the stellate cell synapses in particular may accompany the learning process.

BIOCHEMICAL THEORIES. There are biochemical explanations also for how synaptic 'resistance' might be reduced in learning. Most of these stem from the basic observation that chemical substances like epinephrine and acetylcholine are involved in the transmission of nerve impulses across some synapses; they suppose these or similar chemical events can be made to operate more effectively and that the learning process is explained by the fact that they do so. There is some recent experimental evidence for this view (123).

The post-tetanic-potentiation (PTP) theory should be considered here because many physiologists currently hold that all synaptic transmission is effected through chemical agencies. The physiological definition of PTP is as follows: after prolonged high-frequency (tetanic) excitation of a synaptic region, a test stimulus of fixed strength evokes a larger (potentiated) postsynaptic response. This PTP may last for hours in the animal preparations, although it usually does not, and it has sometimes been suggested that a process similar to that underlying PTP may produce the durable changes in learning (but see 56).

Another suggestion (112) rests on the remarkable advances that have been made in recent years in understanding the biochemical aspects of heredity and neural function. Pointing to the similarities between heredity and memory, its sponsors suggest that the essential feature of learning (or in their words, memory trace) is the formation of geometrically patterned protein molecules in the neurons of the cerebrum.

GLIA CELL POSSIBILITIES. In some quarters interest has been revived in the possibility that the glia cells of the brain may play some important role in learning. These cells outnumber the neurons by at least two to one in the cortex. Very little is known about their function but they are commonly believed to provide mechanical and metabolic support for the neurons. Ramón y Cajal (see 175) thought they might be capable of some movement in which case they could insinuate processes, in an ameboid manner, into the space between pre- and postsynaptic elements at synapses. Presumably this would hinder synaptic transmission. Their retraction might reduce 'synaptic resistance' and enhance conduction. Some recent investigations do show glia cells to be capable of movement while other studies show that they contain a cholinesterase different from that of nerve cells (49). What these facts concerning glia cells have to do with learning remains to be demonstrated.

*Rearranged Neural Circuits*

The second category of theories to explain learning conceives the essential change to be a new arrangement of the way neurons excite one another. It is clear that innate factors cause stimuli to activate certain neural circuits preferentially, but it is also clear that in learning two such preferred circuits become linked in the CR. What is the nature of the link and the new circuit?

RUSSIAN IDEAS. Pavlov's concept of cortical irradiation attempts to deal with this problem. According to this theory excitations arise from CS and US in the cortical areas to which the afferents project (auditory analyzer, optic analyzer, etc.). These excitations irradiate, like the spokes of a wheel, from their points of arrival in the cortex, diminishing in intensity as they spread. The excitations initiated by the CS are the weaker of the two excitations. For this reason they flow toward, or are drawn toward, the center of stronger excitation, i.e. the place where excitations from the US are generated. Then, as a consequence of the repeated presentation of CS and US, a path is worn, so to speak, from the CS center to the US center and the CS comes thereby to bring about the same neural effects as the US.

A modern Russian theory can be illustrated by the ideas of Beritoff (13; 120, p. 56). This will be recounted here in detail because it is not likely to be readily available elsewhere to the reader, although Konorski (120, p. 56) has discussed it. Like Pavlov's notion, its central concept is that excitation irradiates in all directions from the cortical areas excited by US and CS and preferentially along the shortest line between them. However, according to Beritoff, 'two-way' connections come to be formed, specifically between 'star cells' of the two cortical areas and by way of subcortical white matter through the pyramidal association neurons. Ultimately the motor pyramidal cells are influenced to produce movements. "All the star and other neurons with short axons and also all the small (internuncial) and medium sized (association) pyramidal neurons with descending and ascending axons form closed chains of neurons both vertically and horizontally. . . . Neurons forming the pyramidal and extrapyramidal tracts . . . are joined together by internuncial neurons

[and] take part in the formation of neuron chains joining the cortex and the underlying parts of the brain. . . . The entire action of the cortex during both unconditioned and conditioned reflexes is caused by the excitation of certain neuron chains and the more or less considerable inhibition of all the rest. . . . Afferent impulses (thalamic or association) activate the star and other neurons with short axons, on the one hand, and the internuncial and association pyramidal neurons, on the other. . . . In the formation of the neuron chains of the cortex the dendrites of the pyramidal neurons do not take part because they do not conduct excitation to the cells . . . [but] more or less considerable and prolonged potentials may arise [in them].

"By combining two stimulations acting on one and the same or on different analyzers 'two-way' temporary connections are set up . . . among the star neurons . . . by means of the internuncial and association pyramidal neurons. . . . The formation of temporary connections supposes both functional and morphological changes in the cellular elements and in the synaptic apparatus. . . . A cell of one neuron and the synaptic knobs of another neuron lie closer to one another . . . their excitability is noticeably increased and the processes of excitations proceeding in them are intensified. These morphological and physiological changes take place as a result of the interaction of the excitation in all parts of the nervous system but in the cerebral cortex they arise more quickly and last for a longer time, sometimes for life, while in other parts of the brain they are always transitory and pass away soon after cessation of the interaction."

Cognizance does not seem to have been taken in Beritoff's theory of the experiments by Sperry and collaborators showing that knife cuts and the implantation of wires and sheets of mica—devices that destroy intracortical connections and distort whatever electrical fields cortical neurons generate—interfere little or not at all with performance of even complicated CR's (226). Konorski (120) has still other objections to it.

As already mentioned, the idea that stellate ('star') cells in the cortex are of especial importance for CR's is supported by Sarkisov (212, p. 119) who holds that their structural peculiarities "show their specific role in the cortical processes and primarily in the interconnections between the cellular elements of the cortex." He holds, further, "that the cells of the higher parts of the central nervous system and primarily of the cerebral cortex are characterized by considerable lability of form, changing under the influence of external and internal stimulations" (212, p. 120). A report of intracellular changes, twisting of apical dendrites and coarsening of fibers in cortical layers I and II following electrical stimulation is actually available (38). The collection of experimental evidence related to both the anatomical and the neuron chain theories of learning marks much of the current Russian work.

REVERBERATING CHAINS. Another concept of how nerve circuits are rearranged in learning has been called the reverberating chain theory (74, 98, 120). Proceeding from the anatomical fact that neurons are at least potentially connected to other neurons in a reciprocal manner, it supposes that acquisition of a CR consists of setting up a closed circuit of neuronal activity in which neuron A fires neuron B which in turn fires A again. Such chains can include very many neurons. Retention of the CR (or memory) is explained by perseveration of activity in the chain. Hebb (88) supposes that short-term retention may involve reverberating chains only but, if reverberation persists sufficiently in such a chain, the anatomical synaptic changes required to explain long-term memories occur. Many other variants of these popular schemes have been advanced but space will not permit their discussion (61, 131, 132).

### *Theories from EEG Studies*

The most recent theories come from the EEG studies which, as we have seen, are beginning to reveal important new facts. We will consider only one of these, the theory of Gastaut *et al.* (69, 70). It requires rearrangements in at least six separate circuits to explain habituation and conditioning. Both the CS and the US are thought to activate the reticular formation as well as their specific cortical areas, an inference justified by recent neurophysiological findings. Each stimulus, furthermore, activates both a mesencephalic and a thalamic locus in the reticular formation. Habituation consists in the inhibition of both these loci, with consequent disappearance of the alerting response in the scalp EEG. Pairing of a (habituated) auditory CS with (unhabituated) somesthetic US leads to formation of a temporary link in the thalamic reticular formation thus "permitting thalamic collaterals borrowed by the sound signal to act on the neurons previously only activated by the collaterals of the somesthetic signal" (70, p. 31). The mechanism by which CS input

'borrows' the thalamocortical circuit of the US in the thalamus is not elucidated. The theory, despite its emphasis on thalamic changes in learning, is said by its author not to minimize the part played by the cortex. We may consider it to be a somewhat elaborate early attempt to account for the rather meager information that the EEG studies have thus far provided.

*Other Neural Possibilities*

There is a group of theories that explain learning in terms of brain events for which the all-or-none law of nerve action is not particularly relevant. For example, it was once proposed that an increase in the "conductance' of nerve fibers, that is the amount of message each fiber transmitted, might account for learning. This notion was dismissed when nerves were shown to convey all-or-none signals. Recent neurophysiological research, however, establishes the importance of graded events where neurons are in synaptic contact with each other, and so the notion may again deserve further consideration.

In this connection, Bishop (14) points out that the all-or-none activities in the brain serve merely to convey messages from one location to another; they are set up by graded events in the first place and in turn they produce their actions through graded-response processes at the synapses upon which they converge. Grundfest (84) also emphasizes this idea. Graded processes can be maintained at steady states for long times as compared to nerve impulses which vary abruptly from all to nothing. What is needed to explain learning, or at least retention, is long-continued neural events. Since the graded responses in dendrites have appropriate characteristics, it would therefore be in, on or around them that one might look with particular care for neural events peculiar to learning.

Herrick (92, 93) sees in the neuropile an answer to where the integrative processes of learning take place. This neuropile is "a fabric of relatively unspecialized nerve cells and very thin fibers" in which, as an anatomist sees it, the complex events of learning might well occur. Unfortunately he cannot specify what these might be, and so this idea, like so many others, cannot be subjected to experimental test.

By contrast, the cortical 'electrical field' theories that have been advanced from time to time to explain retention in learning (as well as perception in general) can be tested. Electrical conductors have been implanted in and upon the cortex of some animals while insulators have been implanted in others; such devices must have distorted or destroyed very effectively any existing cortical electrical field, yet the complex learned behavior suffered minimally, if at all, as a consequence (226).

*Mathematical Models*

There is one final class of theories to be considered. Certain physicists and mathematicians over the years have been challenged by the complexities of the learning process to develop explanatory formulations for it. Beginning perhaps with Rashevsky in 1938 (201), new contributions at a rate of at least one every year have been made in this area. Recently, with the advent of digital and analogue computers and theory, the rate has been stepped up with the idea, perhaps, that our advancing knowledge of complex switching circuits in machines may have application to the brain. The reader interested in these models of the brain will want to consult the available contributions (11, 56, 97, 100, 240, 241).

*Summary*

A large number of speculations have been advanced to explain the neural correlates for learning. Some of these are based upon a certain amount of objective data about the brain. The most popular schemes incorporate hypothetical changes at synapses with hypothetical reverberating activity in neuron chains. In the large collection of speculations on record, the one (or ones) that will finally harmonize with the facts may well be present but, if so, there is no compelling experimental evidence for it (or them) at this time.

## DISCUSSION AND SUMMARY

This is the appropriate place in our exposition for the authors to propose a comprehensive theory which, without violating any of the data, will explain what happens in the brain during the process of learning. In our opinion, however, this cannot be done at the present time. New information is currently being developed rapidly and, as this happens, the large gaps in knowledge that still exist stand out more and more clearly. Until some of these gaps are filled only the most general of formulations seem warranted. In this discussion, therefore, we shall merely point first to some of the basic questions implied by the material in the preceding sections and then consider one of

the ideas that is presently under active experimental study.

*One Neural Correlate?*

In the literature repeated references are found to the 'neural event' that accounts for learning, as if a single one was envisaged. Yet many theories, as we have seen, postulate two or more to occur (e.g. a synaptic change and a new neural circuit). There seems to be no way to settle the point of single vs. multiple possibilities except by further experiments that will define where in the brain, and when in time, the essential changes occur. Such explanations must harmonize a number of disparate facts about CR's which we will enumerate here.

STRUCTURES INVOLVED. Some Type I habits can be abolished by decortication and then be relearned. The pre- and postoperative CR's seem to be the same and, if we make the plausible assumption that the cortex participated in the original habit, it is evident that the second one is mediated by extracortical structures. The cortex, however, is clearly the site of the durable change in certain kinds of Type II habits. This conclusion emerges, for example, from the experiments in which the corpus callosum was sectioned: in that situation learning is localized to the cerebral hemisphere, and to one side only, for habits involving both tactile and visual discriminations.

Consideration of the time course of acquisition raises another set of problems. A monkey learning to avoid shocks by pressing a lever at a signal appears to pass through a series of behavioral stages in the process. At first the signal arouses much 'emotional' activity, such as piloerection and vocalization. Later, when learning has progressed to 50 per cent correct responses, this 'emotional' behavior can be partly replaced by an 'alert or attentive' attitude. The fully trained animal, in final complete command of the situation, seems undisturbed by the signal and often delays making the correct response until the very last moment.

These successive behavioral stages presumably reflect a progressive reorganization of brain structures or processes during acquisition. If this is true, brain events measured at a particular place in the early stages of learning might be absent there later; while at another brain locus, characteristic brain events might appear only when learning has become complete.

COMPLEXITY. Different amounts of brain seem to be required according to the degree of complexity of the learning problem. If a two-tone pitch discrimination and a three-tone pattern discrimination are taught to a cat, removal of its auditory cortex abolishes both and only the 'simple' pitch discrimination can be relearned. Some neural events responsible for the 'complex' tone-pattern CR have been eliminated by partial decortication but the regions necessary for a 'simple' CR remain.

PHYLOGENETIC EVIDENCE. Learning is common to the octopus and the cat despite the large differences in their neural apparatus (17). In particular the mammalian cerebral cortex is obviously not needed for learning per se.

'EMOTIONAL' LEARNING. In the case of the rat trained both *a*) to press a lever to get a drop of water and *b*) to 'expect' a shock at the termination of a signal, the animal loses only the second of these habits after experiencing a number of convulsive seizures. This experiment defines a clear operational difference between CR's in the intact animal, and it suggests that a corresponding difference exists in the neural basis of 'emotional' as opposed to other CR's.

EASE OF LEARNING. Ordinarily many or very many combinations of CS and US are required to establish a CR, but in the case of imprinting, a single exposure to CS alone produces lifetime retention. The neural events in this exceptional instance, where for a few hours the brain is 'primed' to make a particular set of functional connections might, if understood, also serve for the general case. Perhaps instinctual behavior, like that of newly hatched birds which scatter for cover at the first presentation of specific sounds or moving shapes (238), represents simply the ultimate with respect to such neural processes, namely building them into the organism at the outset so that they need not be formed by learning at all.

*Maturation and Learning*

This brings us to the question of whether or not the neural changes taking place in the normal embryological and postnatal growth of an organism differ from those taking place in learning. Is it possible that they are basically the same and require only slightly different environmental conditions to bring them about?

Innate behavior is distinguished from learned be-

havior on the basis that the first of these emerges in the normal development of the organism while the second appears only through appropriate learning experiences. We will express this dichotomy in terms of maturation vs. learning since many items of unlearned behavior appear after birth and, strictly speaking, are not 'innate' even though they are surely not learned. The important point is that basic patterns of behavior are laid down in the nervous system in the normal development of the system while others are acquired only through learning. In general, the behavior appearing early in the life of the organism is the result of maturation and what emerges later is the result of learning, but the two stages overlap and interact so that learning occurs in some sectors before maturation is completed in others.

'CONNECTIONS'. In both maturation and learning, some change in the nervous system is necessary for 'new' patterns of behavior to occur. It is reasonable to suppose that this change consists of new 'connections' formed between different organs, centers and neurons in the system. The new connection or link, whatever its exact nature, makes possible the flow of messages between points that were formerly 'unconnected.'

In maturation certain parts of the nervous system, as well as the muscles, undoubtedly exert 'attractive influences' on the growth of neural fibers. Somehow or other, motoneurons are guided to their respective muscles and other neurons connect up appropriately with the motoneurons. In addition, sensory neurons will connect up in exactly the 'correct' constellations with nuclei in the central nervous system to perform their functions. And we know that certain portions of the nervous system, for example the medulla, have a controlling and directing influence on the growth of pathways formed in nearby structures.

Some pathways laid down in maturation, when once established, are so rigidly fixed that they cannot be altered. The numerous studies of Stone and of Sperry (225) clearly demonstrate this point. If, for example, a motor nerve of the left leg of the rat is surgically crossed to the right leg, and vice versa, a noxious stimulus to the left leg reflexly evokes lifting of the right leg and no amount of training of the animal corrects this maladaptive response. The animal continues to lift the 'wrong' leg. Similarly, in amphibia, rotating the eyes or transplanting them to the opposite sockets, thus twisting or reversing the animal's visual field, causes the animal to respond to visual objects in a direction opposed to the normal one. Prolonged learning experiences with such visual fields, however, do nothing to alter these inappropriate responses. We are led therefore to conclude that many connections or pathways, once established through maturation, are not easily changed or altered. Those established through learning, in contrast to this, lend themselves easily to formation in the first place and are more or less impermanent.

Although the precise conditions for the formation of the links are different in maturation and learning, there is so far no reason to believe that the processes are fundamentally different. That is to say, it is probably our best assumption at present that the neural changes taking place in maturation and learning are essentially the same and that only the conditions or immediate causes are different.

We might say that maturation rigidly fixes some routes so that unlearned reflexes and responses can be altered little or not at all, and it also prepares other routes so that they can become fixed through the processes of learning. But there is no reason to believe that the central processes that fix behavior in maturation differ from those that fix them in learning.

THE SPECIFIC CHANGE IN LEARNING. What, then, is the specific event that fixes the connections in maturation and learning? So far as maturation goes a number of such factors have been considered; among these are *a*) mechanical, *b*) electrical and *c*) metabolic or biochemical influences upon the direction and state of growth (225). As for the changes in learning, factors of the same general sort have also been postulated, but none of the evidence is critical as we have already seen. We must conclude, therefore, that both the precise mechanism of guidance and control of neurons in maturation, and the exact nature of the specific event in learning are still a mystery.

MOTIVATION AND ATTENTION. Psychologists and physiologists have, from time to time, been led by their observations to infer the existence of many events going on within the mammal during learning. We have considered one of these in detail, namely the idea that some durable change—at synapses or elsewhere—results from pairing CS with US to produce the CR. There are two others, which we will call here 'motivation' and 'attention,' which also appear repeatedly in formal treatments of the problem. An animal 'motivated' to learn (e.g. by reward for success or by punishment for failure) does better than one not so motivated. Similarly, an animal (or a

student) that pays 'attention' to a problem is more likely to solve it than one whose attention wanders. What is the role of these poorly defined and somewhat elusive concepts in the learning process?

MECHANISMS IN MOTIVATION. We know that a hungry rat readily learns to run a maze for food, and that a well-fed one learns the maze imperfectly or not at all. It is generally accepted that both of these observations are related to the fact that, so far as food and water at least are concerned, the animal possesses a built-in mechanism that detects what substance is required for continued well-being and institutes motor activity appropriate for restoring an equilibrium with respect to it. So far as learning goes, we are concerned not with the detection aspect of this process but rather with the way in which such innate mechanisms promote motor activity, for in doing so, they also somehow produce conditions that are favorable for learning to occur.

The hypothalamus is known to contain 'centers' for hunger and thirst. These are defined by the fact that certain hypothalamic lesions produce animals that are continuously ravenous while other lesions produce animals that starve to death in the presence of abundant food (162, 230, 233). For thirst, on the other hand, stimulation of the hypothalamus electrically (83) or with salt solutions (7) elicits dramatically increased drinking behavior. Such observations make it clear that hypothalamic structures connect with the motor apparatus and, under certain conditions, organize and control behavior.

Animals are motivated to learn, of course, otherwise than by hunger or thirst. Electric shocks, for instance, offer powerful motivation and such shocks act, if we can believe our introspections, through pain and the emotional response to pain that they produce. Learning is also commonly accomplished when a pleasant emotional experience is associated with the termination of the training procedure. Thus the emotional repertoire of the animal seems to be implicated in learning in a manner similar to that of 'simple' factors such as hunger and thirst. The question for which we would like an answer is how all these motivating factors—hunger, thirst, emotional mechanisms and the like—prepare the brain for the specific changes of learning.

MECHANISMS IN ATTENTION. Before proceeding to further consideration of this, however, let us examine the concept of 'attention.' It is a common observation in human behavior that we can deliberately pay attention to one stimulus rather than another in a constellation of stimuli. The related ability to emphasize relevant stimuli and exclude irrelevant ones is also clearly an important item in some human learning at least. Similar attentive functions appear to operate in animals as well, and selection of the relevant stimuli and objects in the learning situation may be the first thing an animal does in learning a maze, a discrimination or even a simple classical CR.

In recent times this capacity to attend has been brought into the experimental realm by the studies on the reticular system which are described in detail in Chapter LII by French in this *Handbook* (see also 139, 141). Excitation of the ascending reticular activating substance exerts a general alerting or activating effect on many parts of the brain and particularly on the cerebral cortex. Depression by sleep or drugs leads, among other things, to the dropping out of learned reactions, although unconditioned reactions may still remain (113). Many other examples could be given to show its apparent direct involvement in attentive processes. The reticular formation is not the only part of the brain involved in the reactions we call attention, nor is there any reason to believe that 'causing attention' is its sole function. There is not much question, however, that it plays a major role in the process.

LIMBIC-MIDBRAIN CIRCUIT. How then do the motivating and attentive functions prepare the brain for the specific changes in learning? Recent experiments on the limbic system provide what may be a key to the answer. It is becoming increasingly clear that emotional mechanisms are largely the consequences of activities in the limbic system and hypothalamus (e.g. 146, 147). According to anatomical data recently analyzed by Nauta (173, 174), these structures receive a substantial afferent supply from the nuclei of Gudden and Bechterew in the midbrain reticular formation; the limbic structures project, in turn, back to these same midbrain regions. Thus a major input to, and outflow from, the limbic system involves the midbrain reticular substance which is somehow concerned with attention and alertness, and which also transmits, and modifies the transmission of, impulses passing to and from the cortex. If, as seems reasonable, the limbic and hypothalamic structures are concerned with innate mechanisms in behavior—emotional and otherwise—then the midbrain reticular substance into which they discharge is potentially the place where such neural activity is brought into contact with the neural consequences of current

environmental events. How activity of the neurons of the limbic midbrain circuit would select only some afferent impulses for transmission, which is the process required to explain 'attention,' is by no means clear (but see 108, 142). Neither, unfortunately, can any critical suggestion be advanced at the present time as to how an influence upon, say, the alerting function of the reticular formation would create conditions in the cortex favorable for the specific changes of learning which is our central problem.

The simple scheme outlined here is, however, supported by a sufficient amount of anatomical, physiological and behavioral evidence to make it worth consideration. It does not, of course, account for all the known facts about learning gleaned from any of the experimental sciences. Its main virtue, if it has any at all, is that many experimenters are concentrating their attacks upon it at the present time (see 108, 142, 145, 174). Figure 1 summarizes the anatomical plan that forms the basis of the ideas under discussion here.

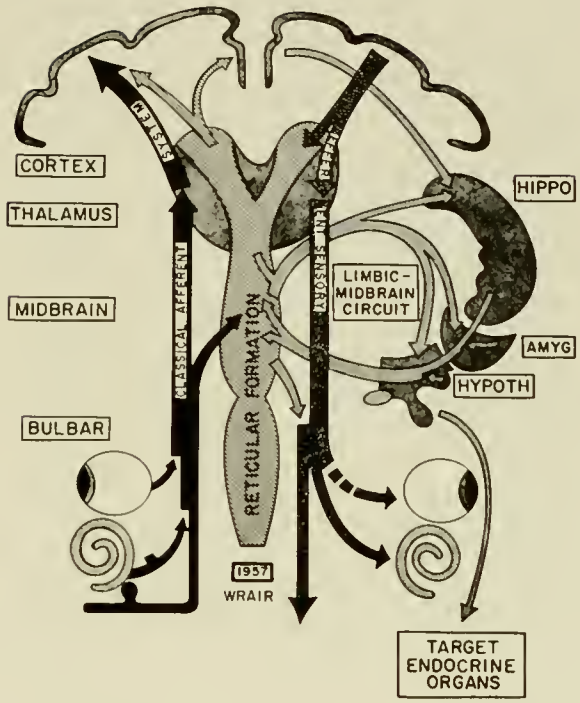



FIG. 1. Simplified anatomical plan of the neural connections involved in learning. The *classical afferent systems* disseminate information about current environmental events to the *cortex* and to the *reticular formation*. *Efferent sensory tracts* originating from these latter structures terminate in the afferent nuclei and even in the sense organs themselves. The *limbic-midbrain circuit*, which starts in, and distributes to, the reticular substance brings the phylogenetically oldest parts of the cortical mantle, as well as the hypothalamus, into functional contact with the rest of the brain structures at a highly strategic point. Experimental information on the vertebrate, while fragmentary as we have seen, is consistent with the idea that each neural structure and circuit outlined here plays its special part as the durable brain change in learning is produced. [U. S. Army photograph.]

*Summary*

At least two classes of events appear to provide the neural basis for learning. One of these includes the durable neural change that constitutes the new link between previously unconnected parts of the brain. Whether this durable change is to be explained by a synaptic change or a new neural circuit, or in some other terms, is still a matter for speculation. Its locus, too, is unsettled. Certainly the cerebral cortex is not exclusively the place where such changes occur.

The second class of neural events in learning consists of those that prime or prepare the brain for the durable change it will undergo. Among these are the so-called 'motivational' and 'attentive' states that commonly precede and accompany the learning process and without which learning is unlikely or impossible. Study of the motivational and attentive mechanisms can be expected to supply at least some of the answers to our questions, for the brain changes they produce underlie the brain change we wish to understand.

Learning is consequently best conceived not as a particular event in a particular place but rather as a sequence of events that involves various organ systems of the brain in a certain order. The end result, to be sure, is the production of a more or less permanent change somewhere, but antecedent events determine where, and even whether, it will occur.

## CONCLUDING REMARKS

People in the past have ruefully commented upon the primitive state of our knowledge about the neural basis of learning and, as this review makes it clear, such comments are fully justified. Our ignorance, however, is not wholly due to lack of industry, as this summary also clearly demonstrates. What, then, have been the main obstacles to progress and what is being done to overcome them?

The major obstacle has undoubtedly been the inability to break through the barrier of the calvarium in order to expose the brain of normal unanesthetized animals to direct experimental investiga-

tion. Within the last few years this barrier has been effectively overcome. Wires can now be placed in practically any desired brain structure, and consequently the study of electrical responses of the brain is no longer limited to the pale and distorted picture provided by scalp electrodes. Similarly with other measurement devices; so long as they are small in size, they can be accurately placed within the neural tissue where the supposed changes occur. This obviously represents a great step forward.

On the behavioral side the development of new techniques of measurement (e.g. the operant methods of Skinner) and the attention being paid to types of learned behavior not previously examined (e.g. imprinting) have appreciably enlarged both the precision and scope of the analysis.

Coupled with these factors are the findings from basic neurophysiology and anatomy that expand the possibilities for investigation and provide a solid base for new experimentally testable learning hypotheses. Put another way, there has been a shift of emphasis in thinking about the neural basis for learning. It is no longer fashionable to conceive of the 'temporary connections' as occurring exclusively in the cortex. At least the reticular substance and the limbic system can in addition be presumed to play important roles, and thus two entirely new parameters are provided along which experimental attacks can be made.

The present era in neurophysiology is therefore unlike any other with respect to the neural basis of learning. As recently as 5 years ago an observer not ordinarily given to pessimism might well have concluded from the available evidence that our search for the answer was permanently doomed. But today, when obviously relevant measurements of many types are being made in the brain substance of unanesthetized animals, an avalanche of entirely new information is about to descend upon us and such a conclusion is hardly justified.

## REFERENCES


1. Ades, H. W. *J. Neuropath. & Exper. Neurol.* 5: 60, 1946.
2. Ades, H. W. and D. H. Raab. *J. Neurophysiol.* 12: 101, 1949.
3. Adrian, E. D., F. Bremer and H. H. Jasper (editors). *Brain Mechanisms and Consciousness.* Springfield: Thomas, 1954.
4. Allen, W. F. *Am. J. Physiol.* 128: 754, 1940.
5. Allen, W. F. *Am. J. Physiol.* 132: 81, 1941.
6. Allen, W. F. *Am. J. Physiol.* 144: 415, 1945.
7. Anderson, B. *Acta physiol. scandinav.* 28: 188, 1953.
8. Anichkov, S. V. *Fiziol. Zhur. S. S. S. R.* 38: 395, 1952.
9. Armington, J. C. and L. L. Mitnick. *Incidence and properties of the kappa EEG rhythm.* Report to the Eastern Psychological Association, New York, April 1957.
10. Artemyev, V. V. and N. I. Bezladnova. *Trudy Inst. Fiziol. (Mosk.)* 1: 228, 1952.
11. Ashby, W. R. *Design for a Brain.* New York: Wiley, 1952.
12. Beck, E. C. and R. W. Doty. *J. Comp. & Physiol. Psychol.* 50: 211, 1957.
13. Beritoff, J. *Trans. Inst. Physiol. (Tbilisi)* 10: 66, 1956.
14. Bishop, G. H. *Physiol. Rev.* 36: 376, 1956.
15. Blough, D. S. *Ann. New York Acad. Sc.* 66: 733, 1957.
16. Blum, J. S., K. L. Chow and R. A. Blum. *J. Neurophysiol.* 14: 197, 1951.
17. Boycott, B. B. and J. Z. Young. *Proc. Roy. Soc., London. ser. B* 143: 449, 1955.
18. Brady, J. V. *Ann. New York Acad. Sc.* 66: 719, 1957.
19. Brady, J. V. In: *Brain Mechanisms and Drug Action,* edited by W. S. Fields. Springfield: Thomas, 1957, p. 111.
20. Brady, J. V. and H. F. Hunt. *J. Psychol.* 40: 313, 1955.
21. Brady, J. V. and W. J. H. Nauta. *J. Comp. & Physiol. Psychol.* 46: 339, 1953.
22. Brady, J. V., L. Schreiner, I. Geller and A. Kling. *J. Comp. & Physiol. Psychol.* 47: 179, 1954.
23. Brogden, W. J. *J. Exper. Psychol.* 25: 323, 1939.
24. Brogden, W. J. and W. H. Ganti. *A. M. A. Arch. Neurol. & Psychiat.* 48: 437, 1942.
25. Bromiley, R. B. *J. Comp. & Physiol. Psychol.* 41: 102, 1948.
26. Bromiley, R. B. *J. Comp. & Physiol. Psychol.* 41: 155, 1948.
27. Brown, C. W. and E. E. Ghiselli. *J. Comp. Psychol.* 26: 287, 1938.
28. Brutkowski, S., J. Konorski, W. Lawicka, I. Stepien and L. Stepien. *Acta Biol. Exper. (Łodź)* 17: 167, 1956.
29. Burns, B. D. *Canad. J. Biochem. & Physiol.* 34: 380, 1956.
30. Buser, P. and A. Roger. *II Congr. Internat. Electroencephalog. et Neurophysiol., Abstr.* 92, 1957.
31. Buser, P. and A. Roger. *I Congr. Internat. Sc. Neurolog.* 417, 1957.
32. Butler, R. A., I. T. Diamond and D. W. Neff. *J. Neurophysiol.* 20: 108, 1957.
33. Campbell, R. J. and H. F. Harlow. *J. Exper. Psychol.* 35: 110, 1945.
34. Carpenter, J. A. *J. Comp. & Physiol. Psychol.* 45: 413, 1952.
35. Cerf, J. A. and L. S. Otis. *Fed. Proc.* 16: 20, 1957.
36. Cherkes, V. A. *Ž. vyš. nerv. Dejat. Pavlova* 5: 415, 1955.
37. Chiles, W. D. *J. Comp. & Physiol. Psychol.* 47: 412, 1954.
38. Cholokashvili, E. S. and A. I. Roitbak. *Trans. Inst. Physiol. (Tbilisi)* 10: 263, 1956.
39. Chow, K. L. *J. Comp. & Physiol. Psychol.* 45: 430, 1952.
40. Chow, K. L. *J. Comp. & Physiol. Psychol.* 47: 194, 1954.
41. Chow, K. L. and P. F. Hutt. *Brain* 76: 625, 1953.
42. Conrad, D. G. and J. V. Brady. *Am. Psychologist* 12: 463, 1957.
43. Crisler, G. *Am. J. Physiol.* 94: 553, 1930.

44. Culler, E. and F. A. Mettler. *J. Comp. Psychol.* 18: 291, 1934.
45. Dashiell, J. F. *Psychol. Bull.* 32: 261, 1935.
46. Deese, J. *The Psychology of Learning* (revised ed.). New York: McGraw-Hill, 1958.
47. Deese, J. E. and W. N. Kellogg. *J. Comp. & Physiol. Psychol.* 42: 157, 1949.
48. Delgado, J. M. R., W. W. Roberts and N. E. Miller. *Am. J. Physiol.* 179: 587, 1954.
49. Desmedt, J. E. and G. La Grutta. *J. Physiol.* 136: 20, 1957.
50. Dews, P. B. and B. F. Skinner (conference co-chairmen). *Ann. New York Acad. Sc.* 65: Art. 4, 1956.
51. Diamond, I. T. and D. W. Neff. *J. Neurophysiol.* 20: 300, 1957.
52. Doty, R. W., L. T. Rutledge, Jr., and R. M. Larsen. *J. Neurophysiol.* 19: 401, 1956.
53. Duncan, C. P. *J. Comp. & Physiol. Psychol.* 42: 32, 1949.
54. Durup, G. and A. Fessard. *Année Psychol.* 36: 1, 1935.
55. Ebbinghaus, H. *Über das Gedachtnis: Untersuchungen zur experimentelen Psychologie.* Leipzig: Duncker und Humblot, 1885.
56. Eccles, J. C. *The Neurophysiological Basis of Mind.* Oxford: Clarendon Press, 1953.
57. Epstein, M. A. and C. T. Morgan. *J. Exper. Psychol.* 32: 453, 1943.
58. Evarts, E. V. *J. Neurophysiol.* 15: 191, 1952.
59. Evarts, E. V. *J. Neurophysiol.* 15: 435, 1952.
60. Ferster, C. B. and B. F. Skinner. *Schedules of Reinforcement.* New York: Appleton, 1957.
61. Fessard, A. E. In: *Brain Mechanisms and Consciousness,* edited by E. D. Adrian, F. Bremer and H. H. Jasper. Springfield: Thomas, 1954, p. 200.
62. Fields, W. S. (editor). *Brain Mechanisms and Drug Action.* Springfield: Thomas, 1957.
63. Finan, J. L. *Am. J. Psychol.* 55: 202, 1942.
64. Finley, C. B. *J. Comp. Neurol.* 74: 203, 1941.
65. Fulton, J. F. *Frontal Lobotomy and Affective Behaviour.* New York: Norton, 1951.
66. Galambos, R. *Physiol. Rev.* 34: 497, 1954.
67. Galambos, R., G. Sheatz and V. G. Vernier. *Science* 123: 376, 1956.
68. Gantt, W. H. A. *M. A. Arch. Neurol. & Psychiat.* 37: 848, 1937.
69. Gastaut, H. *Electroencephalog. & Clin. Neurophysiol.* Suppl. 6: 133, 1957.
70. Gastaut, H., A. Jus, C. Jus, F. Morrell, W. Storm van Leeuwen, S. Dongier, R. Naquet, H. Regis, A. Roger, D. Bekkering, A. Kamp and J. Werre. *Electroencephalog. & Clin. Neurophysiol.* 9: 1, 1957.
71. Gellhorn, E. *Physiological Foundations of Neurology and Psychiatry.* St. Paul: Univ. Minnesota Press, 1953.
72. Gengerelli, J. A. and J. W. Cullen. *J. Comp. & Physiol. Psychol.* 47: 204, 1954.
73. Gengerelli, J. A. and J. W. Cullen. *J. Comp. & Physiol. Psychol.* 48: 311, 1955.
74. Gerard, R. W. *Am. J. Psychiat.* 106: 161, 1949.
75. Gerard, R. W. *Science* 122: 225, 1955.
76. Ghent, L., S. Weinstein, J. Semmes and H.-L. Teuber. *J. Comp. & Physiol. Psychol.* 48: 478, 1955.
77. Ghiselli, E. E. and C. W. Brown. *J. Comp. Psychol.* 26: 301, 1938.
78. Girden, E., F. A. Mettler, G. Finch and E. Culler. *J. Comp. Psychol.* 21: 367, 1936.
79. Giurgea, C. *Stud. Cercet. Fiziol. Neurol.* 4: 41, 1953.
80. Giurgea, C. and J. Drogan. *Stud. Cercet. Fiziol. Neurol.* 5: 367, 1954.
81. Giurgea, C. and N. Raiciulescu. *IV Congr. Internat. Electroencephalog. et Neurophysiol., Abstr.* 98, 1957.
82. Grastyan, E., K. Lissak, F. Kekesi, J. Szabo and I. Vereby. *Kísérletes Orvostudomány* 9: 88, 1957.
83. Greer, M. A. *Proc. Soc. Exper. Biol. & Med.* 89: 59, 1955.
84. Grundfest, H. *J. Neurophysiol.* 20: 316, 1957.
85. Harlow, H. F. and J. Dagnon. *J. Exper. Psychol.* 32: 351, 1943.
86. Harlow, H. F., R. T. Davis, P. H. Settlage and D. R. Meyer. *J. Comp. & Physiol. Psychol.* 45: 419, 1952.
87. Harlow, H. F. and T. Johnson. *J. Exper. Psychol.* 32: 495, 1943.
88. Hebb, D. O. *The Organization of Behavior.* New York: Wiley, 1949.
89. Heistad, G. *J. Comp. & Physiol. Psychol.* 48: 482, 1955.
90. Hernández-Péon, R., H. Scherrer and M. Jouvet. *Science* 123: 331, 1956.
91. Hernández-Peón, R., H. Scherrer and M. Velasco. *Acta neurol. latinoam.* 1: 256, 1955.
92. Herrick, C. J. In: *Publications in Honor of J. Beritoff.* Tiflis: Publ. House, Acad. of Sciences, Georgian SSR, 1956, p. 335.
93. Herrick, C. J. *Evolution of Human Nature.* Austin: Univ. Texas Press, 1956.
94. Hess, R., Jr., W. P. Koella and K. Akert. *Electroencephalog. & Clin. Neurophysiol.* 5: 75, 1953.
95. Hess, W. R. *Vegetative Functionen und Zwischenhern.* Basel: Schwabe, 1948.
96. Hilgard, E. R. In: *Handbook of Experimental Psychology,* edited by S. S. Stevens. New York: Wiley, 1951.
97. Hilgard, E. R. *Theories of Learning* (2nd ed.). New York: Appleton, 1956.
98. Hilgard, E. R. and D. G. Marquis. *Conditioning and Learning.* New York: Appleton, 1940.
99. Holt, E. B. *Animal Drive and the Learning Process.* New York: Holt, 1931, p. 26.
100. Householder, A. S. and H. D. Landahl. *Mathematical Biophysics of the Central Nervous System.* Bloomington: Principia Press, 1945.
101. Iwama, K. *Tohoku J. Exper. Med.* 52: 53, 1950.
102. Iwama, K. and M. Abe. *Tohoku J. Exper. Med.* 56: 345, 1952.
103. Iwama, K. and M. Abe. *Tohoku J. Exper. Med.* 57: 327, 1953.
104. Jacobsen, C. F. *J. Comp. Neurol.* 52: 271, 1931.
105. Jacobsen, C. F. *A. Res. Nerv. & Ment. Dis., Proc.* 13: 225, 1932.
106. Jacobsen, C. F. *Physiol. Rev.* 19: 303, 1939.
107. Jacobsen, C. F. and J. H. Elder. *Comp. Psychol. Monogr.* 13: 61, 1936.
108. Jasper, H., P. Gloor and B. Milner. *Ann. Rev. Physiol.* 18: 359, 1956.
109. Jasper, H. H., L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello (editors). *Reticular Formation of the Brain.* Boston: Little, 1958.
110. Jouvet, M. and R. Hernández-Péon. *Electroencephalog. & Clin. Neurophysiol.* Suppl. 6: 39, 1957.

111. Kappers, C. U. A. *Brain* 44: 125, 1921.
112. Katz, J. J. and W. C. Halstead. *Comp. Psychol. Monogr.* 20: 1, 1950.
113. Kellogg, W. N. *J. Exper. Psychol.* 29: 334, 1941.
114. Kellogg, W. N. *J. Exper. Psychol.* 37: 263, 1947.
115. Kellogg, W. N., J. Deese, N. H. Pronko and M. Feinberg. *J. Exper. Psychol.* 37: 99, 1947.
116. King, F. A. *J. Nerv. & Ment. Dis.* 126: 57, 1958.
117. Klüver, H. *J. Psychol.* 2: 49, 1936.
118. Kogan, A. B. *XX Internat. Physiol. Congr., Communic.* 253, 1956.
119. Köhler, W. *The Mentality of Apes.* New York: Harcourt, 1925.
120. Konorski, J. *Conditioned Reflexes and Neuron Organization.* London: Cambridge, 1948.
121. Konorski, J. In: *Physiological Mechanisms in Animal Behaviour* (Soc. Exper. Biol. Symp. No. 4). New York: Acad. Press, 1950, p. 409.
122. Konorski, J., L. Stepien, S. Brutkowski, W. Lawicka and I. Stepien. *Bull. Soc. Sc. Lettr. Łodź* III: 1, 1952.
123. Krech, D., M. R. Rosenzweig and E. L. Bennett. *J. Cell. & Comp. Physiol.* 49: 261, 1956.
124. Kupalov, P. S. *XX Internat. Physiol. Congr., Communic.* 34, 1956.
125. Lashley, K. S. *Brain Mechanisms and Intelligence.* Chicago: Univ. Chicago Press, 1929.
126. Lashley, K. S. *J. Comp. Neurol.* 53: 419, 1931.
127. Lashley, K. S. *Comp. Psychol. Monogr.* 11: 5, 1935.
128. Lashley, K. S. *Comp. Psychol. Monogr.* 11: 43, 1935.
129. Lashley, K. S. *J. Comp. Neurol.* 79: 431, 1943.
130. Lashley, K. S. *Genet. Psychol. Monogr.* 37: 107, 1948.
131. Lashley, K. S. In: *Physiological Mechanisms in Animal Behaviour* (Soc. Exper. Biol. Symp. No. 4). New York: Acad. Press, 1950, p. 454.
132. Lashley, K. S. In: *Patterns of Organization in the Central Nervous System*, edited by P. Bard. Baltimore: Williams & Wilkins, 1952, p. 529.
133. Lashley, K. S. and L. E. Wiley. *J. Comp. Neurol.* 57: 3, 1933.
134. Leary, R. W., H. F. Harlow, P. H. Settlage and D. D. Greenwood. *J. Comp. & Physiol. Psychol.* 45: 576, 1952.
135. Lesse, H. *IV Congr. Internat. Electro-encephalog. et Neurophysiol., Abstr.* 99, 1957.
136. Liberson, W. T. *Ann. Rev. Physiol.* 19: 557, 1957.
137. Light, J. S. and W. H. Gantt. *J. Comp. Physiol.* 21: 19, 1936.
138. Lilly, J. C. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 705.
139. Lindsley, D. B. In: *Nebraska Symposium on Motivation*, edited by M. R. Jones. Lincoln: Univ. Nebraska Press, 1957, vol. v.
140. Livanov, M. N. and K. L. Poliakov. *Bull. Acad. Sc. USSR* 3: 286, 1945.
141. Livingston, R. B. In: *Brain Mechanisms and Drug Action*, edited by W. S. Fields. Springfield: Thomas, 1957.
142. Livingston, R. B. In: *Handbook of Physiology: Neurophysiology*, edited by J. Field, H. W. Magoun and V. E. Hall. Washington, D. C.: Am. Physiological Soc., 1959, vol. I, p. 741.
143. Loomis, A. L., E. N. Harvey and G. Hobart. *J. Exper. Psychol.* 19: 249, 1936.
144. Loucks, R. B. *J. Comp. Neurol.* 53: 511, 1931.
145. MacLean, P. D. *J. Neurosurg.* 11: 29, 1954.
146. MacLean, P. D. *A.M.A. Arch. Neurol. & Psychiat.* 78: 113, 1957.
147. MacLean, P. D. *A.M.A. Arch. Neurol. & Psychiat.* 78: 128, 1957.
148. MacLean, P. D. and J. M. R. Delgado. *Electroencephalog. & Clin. Neurophysiol.* 5: 91, 1953.
149. MacLean, P. D., S. Flanigan, J. P. Flynn, C. Kim and J. R. Stevens. *Yale J. Biol. & Med.* 6: 380, 1955.
150. Maher, B. A. *J. Comp. & Physiol. Psychol.* 48: 102, 1955.
151. Malmo, R. B. *J. Neurophysiol.* 5: 295, 1942.
152. Marquis, D. G. and E. R. Hilgard. *J. Comp. Psychol.* 22: 157, 1936.
153. McGeoch, J. A. and A. L. Irion. *Psychology of Human Learning* (revised ed.). New York: Longmans, 1952.
154. Meyer, D. R., H. F. Harlow and H. W. Ades. *Am. J. Psychol.* 64: 391, 1951.
155. Meyer, D. R., H. F. Harlow and P. H. Settlage. *J. Comp. & Physiol. Psychol.* 44: 17, 1951.
156. Meyer, D. R. and C. N. Woolsey. *J. Neurophysiol.* 15: 149, 1952.
157. Milner, B. *Psychol. Bull.* 51: 42, 1954.
158. Mishkin, M. *J. Comp. & Physiol. Psychol.* 47: 187, 1954.
159. Mishkin, M. and M. Hall. *J. Comp. & Physiol. Psychol.* 48: 97, 1955.
160. Mishkin, M. and K. H. Pribram. *J. Comp. & Physiol. Psychol.* 47: 14, 1954.
161. Morgan, C. T. *Physiological Psychology.* New York: McGraw-Hill, 1943, p. 457.
162. Morgan, C. T. In: *Nebraska Symposium on Motivation*, edited by M. R. Jones. Lincoln: Univ. Nebraska Press, 1957.
163. Morgan, C. T. and E. Stellar. *Physiological Psychology* (2nd ed.). New York: McGraw-Hill, 1950, p. 439.
164. Morgan, C. T. and W. M. Wood. *J. Neurophysiol.* 6: 173, 1943.
165. Morrell, F. and H. H. Jasper. *Electroencephalog. & Clin. Neurophysiol.* 8: 201, 1956.
166. Morrell, F., L. Roberts and H. H. Jasper. *Electroencephalog. & Clin. Neurophysiol.* 8: 217, 1956.
167. Moss, E. and H. F. Harlow. *J. Psychol.* 25: 223, 1948.
168. Motokawa, K. *Tohoku J. Exper. Med.* 50: 225, 1949.
169. Motokawa, K. and B. Huzimori. *Tohoku J. Exper. Med.* 50: 215, 1949.
170. Munn, N. L. *Handbook of Psychological Research on the Rat.* Boston: Houghton, 1950.
171. Myers, R. E. *J. Comp. & Physiol. Psychol.* 48: 470, 1955.
172. Myers, R. E. *Brain* 79: 358, 1956.
173. Nauta, W. J. H. *J. Comp. Neurol.* 104: 247, 1956.
174. Nauta, W. J. H. *Brain* 81: 319, 1958.
175. Nielsen, J. M. *Bull. Los Angeles Neurol. Soc.* 17: 54, 1952.
176. Olds, J. *J. Comp. & Physiol. Psychol.* 49: 281, 1956.
177. Olds, J. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 671.
178. Olds, J., K. F. Killam and P. Bach-y-Rita. *Science* 124: 265, 1956.
179. Olds, J. and P. Milner. *J. Comp. & Physiol. Psychol.* 47: 419, 1954.
180. Pavlov, I. P. *Science* 24: 613, 1906.
181. Pavlov, I. P. *Conditioned Reflexes.* New York: Oxford, 1927.
182. Pavlov, I. P. *Lectures on Conditioned Reflexes*, translated

by W. H. Gantt. New York: Internat. Univ. Press, 1928.
183. Pavlov, I. P. *Experimental Psychology*. New York: Philos. Libr., 1957.
184. Penfield, W. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer and H. H. Jasper. Springfield: Thomas, 1954.
185. Pennington, L. A. *J. Comp. Neurol.* 66: 415, 1937.
186. Pennington, L. A. *J. Comp. Neurol.* 74, 169, 1941.
187. Pinto, T. and R. B. Bromiley. *J. Exper. Psychol.* 40: 121, 1950.
188. Poirier, L. J. *J. Comp. Neurol.* 96: 209, 1952.
189. Poltyrev, S. S. and G. P. Zeliony. *Ztschr. Biol.* 90: 157, 1930.
190. Popov, C. *Electroencephalog. & Clin. Neurophysiol.* Suppl. 6: 109, 1957.
191. Popov, N. A. *J. physiol., Paris* 42: 51, 1950.
192. Popov, N. A. and C. Popov. *Compt. rend. Acad. sc., Paris* 238: 1912, 1954.
193. Popov, N. A. and C. Popov. *Compt. rend. Acad. sc., Paris* 238: 2118, 1954.
194. Pribram, K. H. *J. Neurophysiol.* 18: 105, 1955.
195. Pribram, K. H. and M. Mishkin. *J. Comp. & Physiol. Psychol.* 48: 198, 1955.
196. Pribram, K. H. and M. Mishkin. *J. Comp. & Physiol. Psychol.* 49: 41, 1956.
197. Pribram, K. H., M. Mishkin, H. E. Rosvold and S. J. Kaplan. *J. Comp. & Physiol. Psychol.* 45: 565, 1952.
198. Prosser, C. L. and W. S. Hunter. *Am. J. Physiol.* 117: 609, 1936.
199. Raab, D. H. and H. W. Ades. *Am. J. Psychol.* 59: 59, 1946.
200. Ramsay, A. O. and E. H. Hess. *Wilson Bull.* 66: 196, 1954.
201. Rashevsky, N. *Mathematical Biophysics*. Chicago: Univ. Chicago Press, 1938.
202. Ricci, G., B. Doane and H. Jasper. *IV Congr. Internat. Electro-encephalog. et Neurophysiol., Abstr.* 90, 1957.
203. Riopelle, A. J. and H. W. Ades. *J. genet. Psychol.* 83: 63, 1953.
204. Riopelle, A. J., R. G. Alper, P. N. Strong and H. W. Ades. *J. Comp. & Physiol. Psychol.* 46: 145, 1953.
205. Riopelle, A. J., H. F. Harlow, P. H. Settlage and H. W. Ades. *J. Comp. & Physiol. Psychol.* 44: 283, 1951.
206. Rosner, B. S. and W. D. Neff. *Am. J. Psychol.* 4: 235, 1949.
207. Rousinov (Rusinov), V. S. and G. D. Smirnov. *Electro-encephalog. & Clin. Neurophysiol.* Suppl. 6: 9, 1957.
208. Ruch, T. C. *A. Res. Nerv. & Ment. Dis., Proc.* 15: 289, 1935.
209. Ruch, T. C., J. F. Fulton and W. J. German. *A.M.A. Arch. Neurol. & Psychiat.* 39: 919, 1938.
210. Rusinov, V. S. *XV Internat. Physiol. Congr., Communic.* 346, 1956.
211. Rusinov, V. S. and M. Y. Rabinovich. *Electroencephalog. & Clin. Neurophysiol.* Suppl. 8, 1958.
212. Sarkisov, S. A. *XV Internat. Physiol. Congr., Communic.* 112, 1956.
213. Shurrager, P. S. and E. Culler. *J. Exper. Psychol.* 26: 133, 1940.
214. Shurrager, P. S. and E. Culler. *J. Exper. Psychol.* 28: 287, 1941.
215. Shurrager, P. S. and H. C. Shurrager. *J. Exper. Psychol.* 29: 217, 1941.
216. Shurrager, P. S. and H. C. Shurrager. *J. Exper. Psychol.* 36: 347, 1946.
217. Sidman, M. *Science* 122: 925, 1955.
218. Sidman, M. *Ann. New York Acad. Sc.* 65: 282, 1956.
219. Sidman, M., J. V. Brady, J. Boren, D. Conrad and A. Schulman. *Science* 122: 830, 1955.
220. Skinner, B. F. *The Behavior of Organisms*. New York: Appleton, 1938.
221. Small, W. S. *Am. J. Psychol.* 11: 133, 1899.
222. Smith, K. U. *J. genet. Psychol.* 51: 329, 1937.
223. Spaet, T. and H. F. Harlow. *J. Exper. Psychol.* 32: 424, 1943.
224. Spence, K. W. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951.
225. Sperry, R. W. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951.
226. Sperry, R. W. and N. Miner. *J. Comp. & Physiol. Psychol.* 48: 463, 1955.
227. Sperry, R. W., J. S. Stamm and N. Miner. *J. Comp. & Physiol. Psychol.* 49: 529, 1956.
228. Stamm, J. S. and R. W. Sperry. *J. Comp. & Physiol. Psychol.* 50: 138, 1957.
229. Stein, L. *Science* 124: 1082, 1956.
230. Stellar, E. *Psychol. Rev.* 61: 5, 1954.
231. Stellar, E., C. T. Morgan and M. Yarosh. *J. Comp. Psychol.* 34: 107, 1942.
232. Stewart, J. W. and H. W. Ades. *J. Comp. & Physiol. Psychol.* 44: 479, 1951.
233. Teitelbaum, P. *J. Comp. & Physiol. Psychol.* 48: 156, 1955.
234. Thompson, R. and W. Dean. *J. Comp. & Physiol. Psychol.* 48: 488, 1955.
235. Thorndike, E. L. *Psychol. Rev. Monogr.* 4, Suppl. II 1, 1898.
236. Thorpe, W. H. In: *Physiological Mechanisms in Animal Behaviour* (Soc. Exper. Biol. Symp. No. 4). New York: Acad. Press, 1950, p. 387.
237. Thorpe, W. H. *Learning and Instinct in Animals*. Cambridge: Harvard, 1956.
238. Tinbergen, N. *The Study of Instinct*. London: Oxford, 1951.
239. Tunturi, A. R. *Am. J. Physiol.* 181: 225, 1955.
240. von Neumann, J. In: *Cerebral Mechanisms in Behavior*, edited by L. A. Jeffress. New York: Wiley, 1951, p. 1.
241. Walter, W. G. *The Living Brain*. New York: Norton, 1953.
242. Warren, J. M. and H. F. Harlow. *J. genet. Psychol.* 81: 45, 1952.
243. Warren, J. M. and H. F. Harlow. *J. Comp. & Physiol. Psychol.* 45: 119, 1952.
244. Wikler, A. *The Relation of Psychiatry to Pharmacology*. Baltimore: Williams & Wilkins, 1957.
245. Wing, K. G. *Am. J. Psychol.* 59: 583, 1946.
246. Wing, K. G. *Am. J. Psychol.* 60: 30, 1947.
247. Wing, K. G. and K. U. Smith. *J. Exper. Psychol.* 31: 478, 1942.
248. Yoshii, N. *Electroencephalog. & Clin. Neurophysiol.* Suppl. 6: 75, 1957.
249. Yoshii, N., J. Matsumoto and Y. Hori. *IV Congr. Internat. Electro-encephalog. et Neurophysiol., Abstr.* 79: 1957.
250. Yoshii, N., P. Pruvot and H. Gastaut. *Electroencephalog. & Clin. Neurophysiol.* 9: 595, 1957.
251. Zubek, J. P. *J. Neurophysiol.* 15: 401, 1952.
252. Zubek, J. P. *Canad. J. Psychol.* 6: 183, 1952.
253. Zubek, J. P. *J. Comp. & Physiol. Psychol.* 45: 438, 1952.

CHAPTER LXII

# Drive and motivation

ELIOT STELLAR[1] | *Institute of Neurological Sciences, University of Pennsylvania Medical School, Philadelphia, Pennsylvania*

CHAPTER CONTENTS



THE NOTION THAT BEHAVIOR is motivated and that the scientific study of motivation might be a profitable approach to the understanding of behavior arose only recently in the history of experimental psychology. From the earliest times, the philosophers concerned themselves with the basic question in motivation by trying to explain the arousal and selective direction of behavior; but their use of theological, teleological and vitalistic conceptions of the 'forces' operative in behavior threw the whole question of motivation into scientific disrepute. Such was the *Zeitgeist* 30 years ago, for example, that Boring was able to write *A History of Experimental Psychology* (25) in 1929 without mention of motivation. It is now possible, however, to look back over history and trace the lines of development of modern approaches to motivation through the contributions of the students of instinct, the experimental physiologists and the physiological psychologists. What emerges is an historical process showing *a*) a gradual replacement of imaginary, explanatory 'forces' by objective, operational definitions of motivated behavior, and *b*) a shift of physiological emphasis from peripheral sensory and hormonal mechanisms to the central neurophysiological mechanisms underlying motivation.

## CLASSICAL INSTINCT DOCTRINE

The earliest scientific thinking about motivation developed with the instinct doctrine. [Beach (19) may be consulted for a recent critical history of instinct.] Unfortunately, much of the idea of motivation was lost in the philosophical effort to maintain the view of man as a unique and free creature of reason and, by sharp distinction, to relegate animal to the control of nature's predetermined instinctive forces. Not until Darwin's emphasis of the role of adaptive behavior in evolutionary survival did the instinct doctrine begin to receive full scientific atten-

[1] This chapter was written while the author held National Science Foundation Grant G-1372 for the study of physiological mechanisms of motivated behavior. Thanks are due to Dr. J. M. Sprague and Dr. Alan Epstein for their helpful comments on the manuscript.

tion and did it become possible to think of human motivation in terms of the simple paradigm provided by the growing study of instinct in animals. Interestingly enough, it was through the efforts of students of personality and social processes, in the work of Freud (58) and McDougall (96), that the concept of motivation re-entered psychology. Freud's conceptions of the 'id,' 'libido,' 'pleasure principle,' 'anxiety' and McDougall's 'propensities' and 'hormic forces' all focused attention on the arousal and direction of behavior, and rooted the notions of instinct and motivation deeply in modern psychological thought.

But even when laid in the foundations of biology by Darwin and pushed into psychology by Freud and McDougall, the concept of instinct still brought objections, for it was all too often used as an explanatory force, and once behavior was labeled instinctive, little was done to investigate it. It was sufficient to say that animals made adaptive responses like building nests and mating because of nest-building instincts and mating instincts, and that man fought and banded together in societies because of instincts of aggressiveness and gregariousness.

In their revolt against the mentalism of the earlier philosophers, the first behaviorists, under Watson (53, 83, 165), rejected the instinct doctrine and with it a large part of the concept of motivation. First, they objected to the use of instinct as an imaginary explanatory force. Second, they rejected instinct because the doctrine implied physiological processes inside the organism, while the behaviorists were trying to account for behavior solely in terms of environmental stimuli and responses and considered instinctive acts merely complex chains of reflexes. Third, the instinct doctrine definitely assumed, contrary to behavioristic theory, that some behavior was not derived from experience but rather stemmed from the organisms' inherited biological characteristics.

The contribution of the behaviorists to psychology is undeniable, for they firmly established objective experimental methods in the study of behavior. But they proceeded in the tradition of their mentalistic predecessors to build a psychology without motivation, without heredity and with nothing more than lip service to the physiological basis of behavior. As Lashley (86) put it, the behaviorists 'threw the baby out with the bath' when they quite rightly rejected instinct as an explanatory force and quite wrongly ignored the biological foundations of important kinds of motivated behavior, simply because they had once been called instinctive.

Two important contributions emerge from this controversy over instincts. *a*) The behaviorists developed an objective operational analysis of motivated behavior without resort to imaginary explanatory forces. *b*) The students of instinct called attention to the fact that motivated behavior is more than a complex response to external stimulation by emphasizing the role of internal physiological states which could determine whether or not external stimuli would be effective.

## CANNON'S LOCAL THEORIES

The first really scientific stride in our understanding of the physiology of motivation came with the efforts of Cannon (40) and his co-workers in the investigation of hunger and thirst. Theirs was an approach from the strict experimental and analytic view point with the definite aim of elucidating physiological mechanisms.

On the behavioral side, Cannon was concerned with only two facets of motivated behavior. One was the initiation of the behavior, and the other was the accompanying sensation that could be reported by human beings. Since he found a correlation between gastric contractions and reports of hunger in his stomach-balloon experiments on man, he concluded that eating was aroused by local gastric contractions which, moreover, provided the physiological basis for the sensation. Similarly, he concluded that local dryness of the throat and mouth was at the basis of thirst sensation. Neurophysiologically, of course, these local theories must mean that receptors are stimulated in the stomach and throat, providing a basis for afferent impulses from these peripheral structures. Other workers, following Cannon's lead, proposed local theories for other kinds of motivation, for example local irritation or pressure arising from the genitals in sexual behavior and local changes in taste-receptor sensitivity in salt hunger.

These local theories were attractive because they seemed to fit human personal experience and because they were so simple in putting their main emphasis on peripheral structures which could be dealt with experimentally. Furthermore, they provided a very easily understandable model for the behaviorists who were trying to understand all behavior in simple stimulus-response terms. When motivation began to enter behavioristic thinking, the theories went something like this: the hungry animal works for food or learns on the basis of food reward because food

reduces or removes the peripheral local stimulation. While the behaviorists decried any reference to subjective experience, it seems unlikely that this theory was hurt by the fact that it implied the removal of 'unpleasant' peripheral stimulation with consequent 'relief' or 'pleasure.'

Despite the general acceptance of Cannon's local theories and their extension and oversimplification by others, in time many cogent arguments against this viewpoint developed. In the first place, human cases were found where sensations of hunger and thirst existed apart from local stimulation. Some people never seemed to experience gastric contractions, yet they ate; people with congenital absence of salivary glands distinguished between their chronically dry mouths and thirst and were able to drink appropriately to their water deficits (150). Furthermore, it was shown that denervation or surgical excision of the stomach did not destroy hunger in man (74, 163) or the regulation of food intake in animals (159) or the animal's ability to work and learn for food rewards (11, 108).

Finally, as further investigations were made into the physiological basis of hunger, thirst, sexual behavior, etc., it became apparent that local stimulation could only be one of several factors contributing to these kinds of motivated behavior. By no means can gastric contractions or local throat dryness, etc. be considered essential in the arousal, maintenance and satiation of such motivated behavior. On the other hand, we have no evidence at present enabling us to deny that local factors make some contribution or even to argue against the possibility that they might provide a most important basis of the sensations accompanying motivation; or that an extremely important part of the motivation of animals working and learning for rewards might not be the reduction or removal of peripheral stimulation. These are matters to be assessed experimentally, and we will discuss some of the relevant studies later.

## HOMEOSTASIS AND SELF-REGULATORY BEHAVIOR

The second important physiological advance in the study of motivated behavior was made in the bold conceptualizations and extensive investigations of Richter (129, 130). A behaviorist with an organismic point of view, he saw that motivated behavior could be of adaptive value in the survival of the organism because of its essential contribution to the maintenance of the internal environment. Starting with the conceptualizations of Claude Bernard and with Cannon's homeostasis, Richter conceived of motivated behavior as self-regulatory behavior in the sense that it may correct deviations of the internal environment in cooperation with the more automatic physiological mechanisms. For example, the warm-blooded animal can regulate its temperature by dietary selection, nest building or simply moving from a hot to a cooler environment or vice versa, as well as by shivering, piloerection, panting, sweating, and vasomotor and metabolic changes. Quite clearly such behavioral responses as these have all the characteristics of motivated behavior, and their investigation has given valuable insight into the physiology of motivation.

In his extensive investigations, Richter was able to show that the organism actually is sensitive to many of its own physiological needs and will develop motivated behavior appropriate to the correction of those needs and the maintenance of the internal environment. For example, he showed that rats were able to select their own diets, cafeteria-style, from a complete array of dietary components (129). Furthermore, shifts in amounts of different substances ingested followed in accordance with prior dietary restrictions, changes in environmental temperature, endocrine gland extirpations, pregnancy, etc. For example, the parathyroidectomized rat ingests abnormally large amounts of calcium and abnormally small amounts of phosphorus, quite in keeping with its physiological needs (127). Similarly, the adrenalectomized rat keeps up its sodium level by ingesting excessive amounts of sodium chloride solutions (126), and so on through many striking examples.

As a behaviorist, Richter saw no advantage in invoking instinct to account for this remarkable behavior. Instead, he sought an explanation in terms of some local expression of the state of physiological need, after the fashion of Cannon's theories, in changes in peripheral receptor mechanisms. Thus, he attributed the strong salt hunger of the adrenalectomized rat to an increase in sensitivity of the salt receptors in the mouth, for the adrenalectomized rat shows a preference for concentrations of sodium chloride solutions so weak that the normal rat fails to select them over water (10, 128). The fact that, following taste-nerve section, adrenalectomized rats failed to select salt and died (129) was taken to support the role of the peripheral receptor change in this motivation, but the defect may have been in the capacity to detect salt rather than in the motivation. As a matter of fact, electrical recording from the

chorda tympani (116) and a study of conditioned responses to salt (41) both show that the normal and adrenalectomized rat have the same very low sensory thresholds for salt in solution. Therefore, the greater salt ingestion of the adrenalectomized rat, even at threshold concentrations but without a change in sensory threshold, suggests that the physiological need must reflect itself elsewhere in the nervous system than in the local, peripheral sensory mechanisms of taste.

Regardless of the mechanism of its influence on the nervous system, the role of the internal environment in motivated behavior is obviously an important one. Yet a number of questions should be asked. *a*) Are there some physiological needs and deficits that do not lead to adaptive motivated behavior? *b*) Are there changes in the internal environment which are not needs or deficits but which can lead to motivated behavior? *c*) Can there be motivated behavior in the absence of internal environment influences? The answer to all three questions is 'yes.' For example, all rats do not grow well in cafeteria-type feeding experiments where they select their own diets (117), and thus far, no specific hungers have been shown for vitamins A and D (67, 168). Actually of course, there is no logical reason why organisms should have specific hungers for every identifiable nutrient in order to survive. In regard to the second and third questions, it is quite evident that motivation can occur without specific deficit or need. There is no internal deficit in sexual and maternal behavior, and the survival of the individual is not at stake, although there are important changes in the internal environment associated with these motivations. Finally, in cases such as the motivation which an animal shows for a nonnutritive substance like saccharin (20) or the motivation to avoid pain, or to manipulate objects or explore a new environment (65), there are no associated changes in the internal environment known to be important in the arousal and maintenance of the motivation.

Thus, not all motivated behavior is self-regulatory behavior, nor is it always of particular adaptive significance in the survival of the individual. The internal environment, important as it is in many remarkable cases of self-regulation, is only one of the factors contributing to the control of motivated behavior. When it does operate, the physiological question becomes: how do changes in the internal environment influence the nervous system and, therefore, behavior? Although local peripheral mechanisms may be the critical targets in certain cases, as Richter and Cannon suggest, it is clear we must look elsewhere in the nervous system for the major effects, presumably in some central neural mechanism.

## MULTIFACTOR CENTRAL NEURAL THEORY

It was Lashley (86) who first put the problem of motivation on a modern neurophysiological basis in his classic paper, 'The experimental analysis of instinctive behavior.' Unlike Cannon and Richter, Lashley gave no special emphasis to local sensory factors in motivation and did not concern himself directly with homeostatic mechanisms, regulatory behavior or needs. Rather he approached the problem of motivation as a student of the central nervous system with the multifactor theory that motivation was the outcome of the joint contribution of many sensory and humoral influences to some central neural mechanism. Although he offered no direct suggestion as to the locus and nature of the central neural mechanism, he made a thoroughgoing analysis of motivated behavior, departing radically from the simple stimulus-response theories of the behaviorists; thereby, he described what the major properties of this central neural mechanism might be.

In his behavioral analysis, Lashley made three important points. *a*) Instincts and motivated behavior are not simply complex chains of reflexes and are not represented by stereotyped acts. The detailed responses involved in mating, nesting, retrieving, etc. vary from individual to individual and occurrence to occurrence. One cannot, therefore, specify a particular motor sequence that characterizes the behavior, for the same result may be achieved by different behavioral means on different occasions. *b*) Similarly, motivated behavior is not dependent upon any single stimulus, confined to a particular receptor locus. Usually, a number of stimuli are effective in a particular sensory or perceptual pattern across several modalities. While a single stimulus might be sufficient to arouse motivated behavior, the adequacy and the intensity of the response are determined by the completeness of a complex pattern of stimulation the animal receives. *c*) Whether stimuli are effective and how effective they are may depend upon sensitization of the organism to particular stimuli by changes in its internal environment. For example, the chronically castrated male rat will not be aroused by the usually effective pattern presented by the female in heat until injected with sex hormones.

That Lashley was on the right track is shown by the

subsequent development and extension of his theories by Morgan (107), Beach (13) and Stellar (151), and by the parallel theories developed by the European ethologists, Tinbergen (158) and Lorenz. In his extensive work on sexual motivation, Beach was able to bring together much experimental evidence in support of Lashley's thesis and did much to make his analysis of sexual behavior a model for the understanding of the physiology of motivation. He was able to show, for example, that sexual motivation actually was under multifactor control, presumably through the joint effects of a number of variables on a central excitatory mechanism which he felt had many of the properties of Sherrington's central excitatory state.

Beach (14, 16, 17) drew the following conclusions from his extensive research and surveys of the literature. *a)* No one sensory avenue is indispensable for the arousal of sexual behavior, for any two sensory systems can be interrupted by peripheral nerve or tract section (auditory, visual or olfactory) or by partial denervation (of genital areas or face and mouth) without destroying sexual motivation in the naive rat. Rather, it appeared that it is a nonspecific minimum of sensory input that is important in determining sexual arousal, just as it seems to be in the activation of locomotion (62). *b)* The neocortex plays a role, but no one part of it is critical in sexual arousal of the male rat, for example, since experiments show that, regardless of locus, the larger the cortical lesion, the greater the deficit in arousal. *c)* Sex hormones also add their effects, for without them, sexual motivation may be greatly reduced or absent; yet it can be restored by hormonal injection. *d)* Learning also makes an important contribution to the arousal of sexual behavior, for previously ineffective stimuli may, through experience, facilitate the arousal of sexual motivation. In sensory deprivation experiments, for example, it may be necessary to interfere with three sensory systems peripherally in the experienced male rat before motivation is eliminated, compared to two in the naive animal. Furthermore, there is evidence that in the male primate, some sexual experience may be essential for the appearance of adult sexual motivation. *e)* That these various factors interact in a common subcortical neural mechanism is suggested by the fact that sexual behavior, lost as a result of neocortical lesions, may be restored by hormone injections. (See p. 1520 on interaction of factors.)

Particularly important in this analysis of sexual behavior are the changes which take place in the control of sexual motivation in phylogeny. Comparing animals from rat to man, there are a decreasing dependence upon hormones, and an increasing dependence upon sensory factors, learning and the neocortex. Sex differences are also important and instructive. The female, for example, is much more dependent upon hormones through the phylogenetic series Beach compared than the male. The male, on the other hand, is much more influenced by changes in sensory stimuli, cortical lesions and learning than is the female.

A somewhat independent development of these views of Lashley and Beach is seen in the contribution of the European ethologists, Tinbergen and Lorenz (cf. 89, 158), in their study of instinctive behavior. This theory of instincts perhaps suffers because it is not based on modern neurophysiological principles but rather is cast in hydrodynamic terminology. Thus, Tinbergen speaks of neural mechanisms controlling instinctive acts which build up a 'reservoir' of 'action specific energy' until released by some appropriate stimulation. No direct effort at localization or experimental manipulation of the neural mechanism is as yet apparent in this work. But this criticism is of only minor concern at the moment, for it would be quite possible to recast Tinbergen's terminology and make a direct experimental approach to the neurophysiological problem.

Like Beach and Lashley, the ethologists propose that changes in the internal environment, such as those produced by deprivation or an increase in sex hormones, contribute, along with sensory influences, to the arousal of a central neural mechanism. In some instances, internal changes may be intense enough to yield instinctive patterns, in the absense of sensory stimuli, in which case the ethologists speak of 'vacuum reactions.' But usually, sensory stimuli play two essential roles: *a)* they contribute to the level of excitation in the central neural mechanisms, and *b)* they 'trigger' the response by releasing the excitatory mechanisms from the control of a postulated inhibitory mechanism; in this latter case, the stimuli are called 'sign stimuli' or 'releasing stimuli.'

On the basis of their analysis of complex instinctive acts into behavioral hierarchies, the ethologists furthermore assume that there is a hierarchy of neural mechanisms, each built up by internal and sensory influences and each selectively released from inhibition by appropriate stimuli. The release of each neural mechanism not only results in a behavioral expression but also 'primes' the next lower neural mechanism in the hierarchy by contributing to its excitation along with sensory and humoral factors. Thus in the reproductive behavior of fish, for example, the sequence

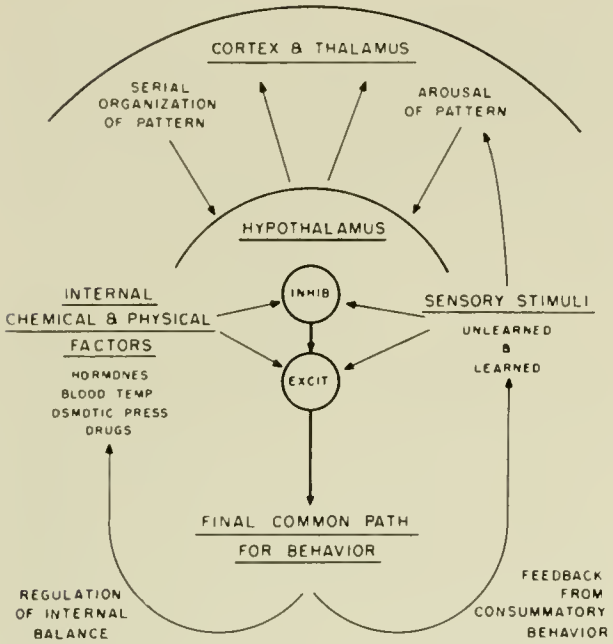



FIG. 1. Schematic diagram of the physiological factors contributing to the control of motivated behavior. Description in text. [From Stellar (151).]

is started by hormonal triggering of the highest neural mechanism which yields migratory behavior. Then, as new stimuli in the environment are encountered, excitation in a succession of lower neural mechanisms is built up and released by sign stimuli specific to selection of territory, nest site and nesting materials, fighting in territorial defense against intruders, mating and care of the young.

While the neurophysiological propositions of the ethologists are quite speculative, their behavioral analyses have been excellent and will provide a basis for direct physiological investigations of the mechanisms underlying motivation. Their work makes possible the extension of Beach's phylogenetic comparisons to inframammalian species and to kinds of motivation other than sexual. Furthermore, they offer rich insights into the organization of motivated behavior because of their insistence upon relatively complete descriptions of patterns of motivated behavior as observed in naturalistic settings, in contrast to the American psychologists' relatively artificial laboratory testing of isolated segments of behavior.

One thing should be apparent now about all of these central neural theories; they are based largely on inferences from behavior, for they fail to take into account direct studies of the central nervous system which might provide experimental evidence relevant to the locus and properties of the postulated central neural mechanism. Fortunately, there is now a large and growing body of experimental data on the role of certain central neural structures in the arousal and integration of motivated behavior, and it is possible to use this information in a specific and physiologically concrete extension of the theories of Lashley and Beach. This was done originally in 1954 by the present author (151) in an effort to arrive at a unified multifactor theory of motivation, general enough to apply to many different kinds of motivation, across many different species of animals. A brief summary of this theoretical view will be given here in order to provide an up-to-date physiological framework for the review, later in this chapter, of the experimental evidence we now have available on the physiological basis of motivation.

A schematic diagram of the physiological mechanism believed to underlie motivation is shown in figure 1. Look first at the diencephalic mechanism in the middle of the diagram. As far as we can tell from present experimental evidence, the major focus of the neural system or the integrating mechanism responsible for the arousal, execution and satiation of motivated behavior lies in the diencephalon, probably the hypothalamus. Since ablation and stimulation of restricted foci in this region of the brain result in either increases or decreases in motivated behavior, it appears, furthermore, that it may contain two kinds of functional areas which can be described operationally as excitatory and inhibitory mechanisms. The basic assumption here is that the arousal of motivated behavior is determined directly by the output of the excitatory mechanism, and the satiation of motivated behavior by the output of the inhibitory mechanism. Thus, there is believed to be a reciprocal mechanism which provides a basis for refined and graded control of motivated behavior. Whether the inhibitory mechanism acts only on the excitatory one as suggested in some experimental work, and shown in the diagram, or whether the two mechanisms exert their effects on a common mechanism for the execution of motivated behavior is still an open question.

In any case, starting with this dual diencephalic mechanism, the question then becomes: what controls its activity and therefore the arousal, execution and satiation of motivated behavior? As Lashley and Beach suggest, the behavioral evidence implies that three classes of factors are operative. *a*) Sensory influences, operating through afferent pathways, physiologically defined as specific and nonspecific, may

arouse these diencephalic mechanisms directly or indirectly. On the one hand, as Beach suggests, these sensory influences are additive in their effects, so that it is the sum total of sensory input to these diencephalic mechanisms that determines the amount of arousal or satiation. On the other hand, sensory influences must contribute highly specific information, for motivated behavior may be highly discriminative and selective. Furthermore, as Beach points out, sensory influences may be classed as learned or unlearned, for previously ineffective stimuli can come to arouse or satiate as a result of past experience. *b)* Chemical and physical properties of the internal environment, operating through the circulatory system and through the cerebrospinal fluid system, presumably can contribute directly to the activity of these excitatory and inhibitory mechanisms and, therefore, to the arousal and satiation of motivated behavior. Again, while these humoral influences may have general arousing and depressing effects, there is evidence to suggest that their effects may be highly specific to particular types of motivated behavior, implying the possible existence of highly selective central 'receptors,' sensitive to changes in the internal environment. *c)* Finally, central neural influences, arising elsewhere in the nervous system, particularly the neocortex and the rhinencephalon, may contribute excitatory or inhibitory effects to the control of the diencephalic mechanisms and, through them, play a role in the serial organization and patterning of motivated behavior, as well as its arousal and satiation.

While the factors operating in the control of motivation can be listed simply, their mode of action is undoubtedly complex. In the first place, all of these factors probably interact in their influences, being interdependent and perhaps equipotential in the arousal of the basic diencephalic mechanisms. Thus, their combined influences might be thought of as additive such that an increase in one influence would compensate for a decrease in another. For example, how effective a given sensory stimulation will be in arousing motivation will depend upon the concomitant influence of the internal environment or upon the nature of previous stimulation whether learned or unlearned.

In the second place, it is possible that each of these factors could have two kinds of influence on the diencephalic mechanisms; they could either activate or depress either excitatory or inhibitory diencephalic structures. This results in an enormous increase in the possibilities for refined control and for complexity of mechanism. A sensory stimulation, a neocortical or rhinencephalic influence, a hormone, or a drug, for example, could decrease motivated behavior by activating the inhibitory mechanism or depressing the excitatory mechanism.

A third complexity in this mechanism derives from the fact that the execution of the motivated behavior itself can provide important sensory changes and changes in the internal environment (see the lower part of fig. 1). Where materials are ingested by the organism as in hunger and thirst, there is a continuous change in the internal environment due to absorption once the behavior starts, and throughout, there is obviously a new source of stimulation of the alimentary tract upon ingestion. In addition, even where there is no ingestion, as in pain avoidance or in nest building, there is feedback of response-produced stimulation occasioned by the execution of the behavior as well as changes in stimulation resulting from changes in the environment produced by the behavior.

As you will see later, there is much experimental evidence for many parts of this conceptualization, but there are still many gaps in our knowledge and it is not clear that all the details of this general mechanism apply to all cases of motivated behavior. For example, we cannot be certain even at present that the major focus of the neural system controlling motivation actually is in the hypothalamus (69). Even in cases where the hypothalamus is implicated our information is still incomplete. There seems to be no humoral factor in the motivation to avoid noxious stimuli; no inhibitory mechanism in the diencephalon has yet been discovered for thirst, although one has been shown for hunger; very little is known about cortical mechanisms in hunger, although a great deal has been worked out relative to sexual behavior, maternal behavior and emotions. Furthermore, there is a real question of how much of this theoretical mechanism may be operative in learned motivation, and in certain complex instances of human social and personal motives. As Beach has shown in the case of sexual motivation, it is clear that the relative contributions of the factors controlling motivated behavior change in phylogeny. Obviously, the specific physiological mechanism for each kind of motivation, and for each species, will be unique in some way; but the point here is that all motivation should have the same general, multifactor physiological mechanisms at its basis.

Before going into the experimental evidence summarizing our knowledge of the physiology of motivation, it will be helpful to digress in order to specify more precisely what we mean by motivation in be-

havioral terms and how we may measure motivation experimentally.

## BEHAVIORAL DEFINITION OF MOTIVATION

In order to approach this difficult task of analysis and definition of motivated behavior, it will be helpful to start with two simple examples of motivation. This first is an instance cited by Lashley (86) of the motivation to ingest *Hydra* seen in the round worm, *Microstoma*. This worm uses stinging cells to capture prey and in its defense, but it must acquire these cells from *Hydra*. When *Microstoma* has lost its stinging cells, it ingests *Hydra* voraciously. As stinging cells are accumulated, they are evenly distributed around the surface of the body, and triggering mechanisms are grown out to them. A point is reached, however, when *Microstoma* has a full complement of stinging cells and it no longer ingests *Hydra*, even in the complete absence of all food sources.

Illustrated here are a number of basic concepts of motivation. The first is the concept of 'physiological need,' represented in this case by a lack of stinging cells. Second is 'drive' shown by the increased activity of *Microstoma* in the face of its deficit. Third, there is 'goal' and 'goal-directed activity' represented, respectively, by *Hydra* and by the specific selective activity *Microstoma* shows in the approach to and ingestion of *Hydra*. Fourth, is 'satiation' shown by the failure of *Hydra* to elicit further specific goal-directed activity, and the reduction of general activity in *Microstoma*, or its quiescence, once it has corrected its deficit of stinging cells.

The same concepts derive from a second example, a case of salt hunger in a three-year-old child unable to retain salt because adrenal tumors caused an insufficiency of adrenal cortical hormones (169). Here the physiological need is the salt deficit; this child was restless and agitated, especially during feeding, indicating an undirected drive. The goal of salt became apparent in the child's marked preference for bacon and soda crackers from which he licked the salt. The goal-directed behavior became even more obvious when the child accidentally discovered the salt shaker and ate salt by the teaspoonful. He then learned to ask for salt in his prelanguage years by screaming and pointing to the cupboard where salt was kept; it is perhaps significant, moreover, that his first word was 'salt.' Following bouts of salt ingestion, the child showed satiation; he was no longer interested in the salt shaker, he no longer preferred salty foods, and his general appetite improved. Of course, as salt was lost from the body, the need returned and the whole cycle repeated itself. In this way the boy managed to keep himself alive until he was brought to a hospital for observation and unfortunately was placed on a normal salt diet which kept him alive for only 7 days.

These two examples are particularly interesting because they show how the same kind of behavioral analysis applies over a wide range of the phylogenetic scale, up to and including man. Furthermore, in contrast to the first, the second example illustrates quite clearly the role of learning in the organization of motivated behavior, particularly in the selection of goals and in the use of specific responses, among them language, as instrumentalities in the development of goal-directed behavior.

Not all instances of motivated behavior fit this pattern completely nor is it a simple matter to go from this behavioral analysis to experimental investigation of underlying physiological mechanisms. But it is possible to make some headway in this direction and, at the same time, to evaluate these behavioral concepts in the light of physiological data and theories.

### *Need*

The concept of physiological need was a valuable one in the past, for it gave the study of motivation biological roots. Classically, it has been specified as some physiological deficit or imbalance in the internal environment that, in the extreme at least, would endanger the life of the organism (130). Unfortunately, however, the term has been badly abused and overworked. First of all, need has lost some of its biological significance for it has been inferred by some workers in almost every kind of motivation, without any physiological reference (111). Moreover, as we have already pointed out, not all physiological needs lead to motivation and not all motivation derives from needs or deficits. From a physiological point of view, furthermore, specification of an internal environment factor in the control of motivation is far more inclusive than a concept of need. And finally, as you will see in a moment, the concept of drive can easily be substituted for need at the behavioral level. Thus, it appears that the historical concept of need is superfluous, and perhaps misleading, in the analysis of motivation and should be dropped from use.

### *Drive*

Drive is a purely behavioral concept that refers to the intensity of motivated behavior, regardless of how

it is measured, whether it is the amount of general activity an animal shows, the amount of ingestion, the amount of work done to overcome a barrier to a goal, or the frequency, speed or magnitude of a response instrumental in reaching or avoiding a goal. Although drive has been used in the past to refer to animistic forces which propel or energize the motivated animal, its value in modern usage is that it can be specified quantitatively and operationally by a variety of experimental measures which we shall discuss below. It should also be mentioned at this point that drives may be learned in the sense that previously neutral stimuli may elicit an increase in any of the measures of drive after appropriate experience. Thus, a rat will learn to work hard to escape a weak visual or auditory stimulus that has previously been followed by electric shock (97). Or a chimpanzee will work for a poker chip that can later be used to obtain food (170). From a physiological point of view, drive, whatever its origin, must be equivalent to the degree of activation or arousal of the excitatory neural mechanism operating in motivation. While there is some evidence supporting this assumption, much experimental work is needed before the mechanism of drive can be specified in any detail.

*Goal*

The goal of motivated behavior is not always easy to specify. In a simple case, it may be some specific object which the organism approaches or avoids selectively and acts upon with a particular pattern of behavior, like a mate or a noxious stimulus. In some cases, however, there may be no specific identifiable object as in sleep, a burst of running activity or exploration; and even where there is a goal object, part of the goal, at least, may be simply the stimulation arising from the execution of a pattern of response. Experimentally, a goal is identified when, following attainment of the goal object or execution of the goal response, there is a reduction of drive and eventually satiation. In addition, where specific goal objects are involved, the goal is also indicated by the organism's selective orientation to it, either approach or avoidance.

We will discuss both satiation and goal-directed behavior in a moment. At this point, it is worth noting that once a goal is reached or an animal has had previous experience with it, it may function to increase drive, depending upon the nature and pattern of stimulation the goal provides. For example, a 10 per cent glucose solution will elicit more consummatory behavior and more work, even when ingestion is relatively negligible, than a 5 per cent glucose solution (64, 95). Behaviorally, then, we may speak of the 'incentive-value' of the goal; physiologically, this is presumably correlated with its relative contribution to the arousal of the excitatory neural mechanism involved in motivation.

A suitable goal may be used to promote learning or maintain performance in a motivated animal, as in the case of the animal learning to run a maze to reach food. In this instance, we refer to the goal as a 'reward.' Rewards and 'punishment' in the case of noxious stimuli are also called positive and negative 'reinforcements' to signify their effects in strengthening learning and performance when appropriately applied in an experiment. Furthermore, as you might expect, goals may be learned, as in the case where the poker chip becomes the goal of the chimpanzee's efforts. Then we speak of 'acquired goals' and secondary rewards and secondary reinforcement in contradistinction to primary rewards and primary reinforcement which require little or no learning to be effective. We know relatively little about the physiology of learning but, in cases like these, presumably the central neural mechanism in motivation plays an important role. Later in this chapter, we shall discuss briefly some direct experimental approaches to the physiology of reinforcement.

*Goal-Directed Behavior*

This is the specific pattern of behavior, associated with a particular kind of motivation and elicited by specific environmental stimuli. From an objective point of view, this is the appetitive behavior of the students of instinct; the appetite of the physiologist and psychologist; the pleasure seeking and pain avoidance of the philosopher and the psychologist; the preference, choice, the approach, avoidance, the selective behavior of the experimental psychologist.

Orientation to a goal involves two major aspects. One is the selective perception of the goal. In the motivated state, the organism is particularly sensitive to certain facets of the environment, as in the response of the maternal organism to its young or the male rat to the female in heat. The other is that, in the motivated state, certain response patterns are facilitated, in the extreme case of very strong motivation, to the point where the goal-directed response may be emitted 'spontaneously' or at least upon minimal stimulation, the so-called 'vacuum-reactions' of Tinbergen and Lorenz.

As we have already pointed out, the same goal may be reached by different behavioral means at different times. This variability in goal-directed behavior is greatly increased by learning new instrumentalities to attain goals and in learning new goals. Thus, a rat may learn to escape or avoid electric shock by depressing a lever, turning a wheel, standing on its hind legs, leaping over a hurdle, running through a white rather than a black door (146). Or it may be taught one arbitrary response to obtain food and another to obtain water (88), showing not only specific instrumentalities appropriate to each motivation but also a precise discrimination of its own motivational states. In addition to such selective learning of new instrumentalities, the animal, of course, may also learn new goals, thereby expressing its motivation in new ways, not involving consummatory behavior or other natural patterns of expression.

*Satiation*

Satiation or satiety refers to the reduction of motivated behavior following the achievement of a goal. Subjectively, this is relief from pain, satisfaction or pleasure; or it may be loss of interest or indifference. Operationally, it is the reduction of the organism's drive, its general activity and restlessness, and its specific goal-directed behavior. Since an animal is typically under the influence of many motivations at once, reduction in the expression of one motivation may be due, in part, to the interference resulting from the expression of other motivations. The thirsty animal, for example, drinks steadily until it is presumably forced to rest in response to fatigue; after a brief rest, it returns to drink some more, and then rests again. As the tendency to drink reduces even more, the animal may turn to food and eat instead of drink. Then it may drink briefly again, then groom itself. Eventually, it may sleep, presumably a response to still another motivation (152). So satiation must be thought of not only in terms of direct reduction of drive and goal-oriented response, but also in terms of the competition of motives.

Physiologically, we are not sure what satiation is. As suggested earlier, it can be thought of most simply as an increase in the activity of inhibitory mechanisms in the diencephalon which lead directly or indirectly to a reduction in the activity of the central excitatory mechanism or a counteraction of its effects. Presumably, correction of a deficit in the internal environment may lead to satiation; some evidence suggests that merely the execution of a pattern of motivated behavior feeds back stimulation which contributes to satiation; fatigue and sensory adaptation may also enter as factors, and learning may possibly enter. The problem of what factors contribute to satiation is something on which we have some evidence, but it is still a major experimental question and we have yet to work out the details of the neurophysiological mechanism involved.

*Motivated Behavior*

In terms of this analysis, then, motivated behavior includes three major behavioral processes: the arousal of drive, goal-directed activity and satiation. Physiologically, these are the problems of: *a*) activation of an excitatory mechanism by internal states, and learned and unlearned sensory influences; *b*) the basis of the change in sensitivity and reactivity of the organism to patterns of sensory stimuli, and the mechanisms responsible for the organization and facilitation of the patterns of response involved in the specific execution of the motivated behavior; and *c*) the activation of an inhibitory mechanism by internal states, and learned and unlearned sensory influences.

Behaviorally, the experimental study of motivation requires: *a*) the measurement of drive or the intensity of motivated behavior; *b*) the analysis and measurement of goals, their effectiveness and their modifiability through learning, and the measurement of selection, choice or preference in the execution of specific goal-oriented behavior and the modification of these specific responses by learning; and *c*) the specification of the conditions under which satiation will occur and the measurement of its magnitude, especially taking cognizance of the competition among motives. Some of these problems will be taken up in the next section; then we will go on to address the physiological problems.

## BEHAVIORAL MEASURES OF MOTIVATION

As you can see from the complexity of many of the concepts arising in the analysis of motivated behavior, it is extremely important to anchor them experimentally by use of operational definitions. To a large degree, this is the problem of the experimental measurement of behavior. Therefore, at this point, it will be helpful to review the methods that have been used to specify motivated behavior and to measure its various facets.

*General Activity*

The most general measure of motivation is to record gross bodily activity. This measure is simply a quantitative record of the intensity of behavior and as such serves primarily as an index of drive. While many factors influence bodily activity, and not every change in activity is a change in drive, it is nonetheless possible under appropriate experimental conditions to show that changes in activity do reflect changes in drive.

Two somewhat different kinds of general activity have been recorded. The one most often used is gross locomotor activity. This is the measure obtained when a rat runs in a rotating drum or activity wheel (110), or when an animal is tethered to a counting device (84). The second measure is of restless activity, recorded in a tambour-mounted (125) or spring-suspended cage (73), the tilting cage (26), or the cage divided by a photoelectric beam (142), where small as well as large movements may activate the recording system. In addition, there are several other kinds of activity which can be recorded and which have been seen particularly following certain brain lesions: stereotyped pacing back and forth (133), forced circling (78), forced following of visual stimuli (77, 144) and obstinate progression (7).

A number of studies show a systematic relationship between changes in drive and changes in activity. In the female rat, for example, activity increases during estrus, when estrogen levels and sexual receptivity are high, and decreases during diestrus (162). Where a rat is deprived of food or water or both, or of certain vitamins, activity increases steadily as deprivation proceeds, reaching a peak and then falling off as the animal becomes physically impaired (23, 161). This peak may be as much as five times basal activity and is reached after 5 days of food or water deprivation, 2 days of both food and water deprivation, and 10 days of vitamin deprivation. That the factor of physical impairment may be specific to the locomotor activity measure is suggested by the finding that gonadectomy reduces running activity by 90 per cent (72), while it results in only a 10 per cent decline in restless activity (73).

In addition to physical impairment, there are other variables, not necessarily related to drive, which also influence activity. In a number of different experiments, it has been found that: *a*) activity is related to daily light-dark cycles, the rat, for example, displaying most of its activity at night (37); *b*) activity is high in low environmental temperatures and low in high temperatures (38, 39); and *c*) it is possible to breed selectively for activity (134).

Accordingly, while the association between activity and drive is an empirical fact, successful use of gross bodily activity as an index of drive depends upon careful control of conditions of measurement. This is particularly true because learning and other sources of individual differences make the activity measures very variable. For example, it may take some animals from 10 to 25 days of constant opportunity to run in wheels before they run at all, and it may be over a month before animals kept on a restricted feeding schedule reach a stable base line of daily running (124). Furthermore, these individual differences may be quite large in absolute magnitude, some rats running over 20,000 revolutions a day (over 10 miles) while others may never exceed 200 revolutions a day.

Despite all these shortcomings, we may conclude that gross bodily activity is a function of the amount of drive and that, under appropriately controlled conditions, increases in drive are reflected in increases in activity up to the point where the animal is physically impaired.

*Consummatory Behavior*

The most commonly used measure of motivation in physiological studies is the goal-directed consummatory response, idealized in the examples of food ingestion and water intake. In these two instances, the experimental procedure is to measure the amount consumed in some standard test situation where the animal is, ideally, but not necessarily actually motivated in just one way (e.g. deprived of water) and is limited in its choice of responses to one goal (water). In addition, the animal is usually given the opportunity to habituate to the test situation emotionally and to adapt to the physical and temporal circumstances of testing. Under such conditions, it has been shown that the amount of water ingested is a function of the amount of deprivation. Rats, for example, will drink more and more water following longer and longer deprivations up to the 8th day of deprivation when they will succumb (152). No in-between point of physical impairment where water intake falls off after reaching a peak has been reported as in the case of other measures of motivation, like running activity or performance in the obstruction box (see below).

Detailed analysis of the course of water intake gives further insight into thirst motivation and shows the complexity of even simple consummatory response

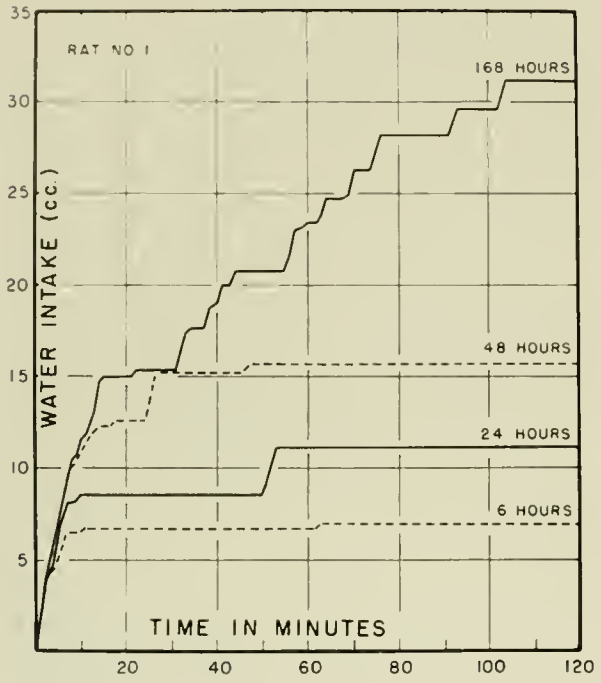



FIG. 2. Continuous records of the drinking behavior of one rat after different amounts of water deprivation, showing how this type of consummatory behavior tends to be an all-or-nothing response with alternations of constant rates of drinking and resting. [From Stellar & Hill (152).]

measures (152). Rats lap water at the constant rate of 6 to 7 laps per sec., netting 0.004 to 0.005 cc per lap. The only thing that changes during drinking, and as a function of deprivation, is the duration of bursts of lapping and the length of pauses. At the outset of drinking, lapping is steady for a maximum of about 8 min.; then it is interrupted by a brief pause (fig. 2). As time goes on, the bursts of steady drinking decrease in length and the pauses increase. Observation shows that the pauses are due to the interference of other motivational tendencies with drinking: fatigue, grooming, exploration, sleep. The weaker the thirst, the more readily these other tendencies interfere and, therefore, the sooner and more frequent the pauses and the greater their length.

The magnitude of the consummatory response is determined by the nature of the goal as well as the amount of deprivation. This is illustrated most clearly in the case of specific hunger for sodium chloride. Here, the amount of salt solution ingested as well as the absolute amount of sodium chloride is a function of the concentration of the solution (see fig. 4) as well as the animal's salt deficit (55).

The concept of consummatory behavior changes considerably where the motivated behavior does not involve ingestion. In sexual and maternal behavior, for example, the consummatory response is often specified as an 'innate reflex pattern,' such as the execution of the copulatory response or nest building, retrieving and care of the young, for these are biologically useful goal-directed patterns that presumably lead to drive reduction or satiation. In the sexual behavior of the male rat, the consummatory response is measured in terms of the latency and frequency of mounting, pelvic thrusts, intromissions and ejaculations. The strength of these responses is determined by the concentration of sex hormones, the adequacy of the stimulus animal and previous experience (14, 16). With the female rat, the acceptance of the male, the degree of completeness of the pattern of lordosis, rump elevation, tail deflection and ear wiggling, as well as the latency and frequency of these responses to the male serve to indicate the strength of consummation (14, 16). In this case, hormonal concentration is critical. In maternal behavior, the frequency and persistence of retrieving, the promptness in moving a nest from a blast of cold or hot air, the completeness of nest building, etc., all are measures of the strength of drive or consummation. The strength of these responses is determined primarily by the stimulus provided by the young and, to some extent perhaps, by hormones (18, 87).

Specification of the consummatory response becomes still different in cases like the avoidance of noxious stimuli, sleep, exploration, fighting, etc. where a specific response pattern is often more difficult to describe. In fact, there is some question as to whether or not it is possible to use the term consummatory behavior meaningfully where there is no ingestion. The argument in favor of extending the concept is essentially that consummatory responses are the 'natural,' adaptive, goal-directed responses of the animal, not critically dependent upon learning, although modifiable by experience. However, as Miller (99) has pointed out, other measures of motivation do not always give the same results as the consummatory measures and, therefore, we must be careful not to base too many of our conclusions about the physiology of motivation on consummatory measures alone. Quite clearly, the different measures get at different facets of motivation and probably will reveal different aspects of the underlying physiology. This does not detract, however, from the great value of the consummatory behavior measure.

*Obstruction Method*

Because even the simplest expression of motivation involves work, fatigue and other competing motives, it is possible to look at the consummatory response and other measures of motivated behavior as the strength of the tendency to overcome some interference in reaching a goal. This principle is put directly to work in the obstruction method. Here the motivated animal is required to cross some barrier to reach its goal. In the case of the rat, the barrier might be a physical obstruction, such as a tunnel filled with sand, a doorway blocked with many thicknesses of paper or an electrified grid which the animal must traverse. In the first two cases, the animal must work to reach its goal; in the last, it must take punishment. In all of these methods, the frequency with which the barrier is crossed in unit time, the speed of response and the size of the barrier necessary to inhibit goal-directed behavior completely are all measures of the strength of drive.

The obstruction box with an electrified grid was developed by the Columbia workers under Warden (164) and used as a standardized test for the measurement of many kinds of motivation in the rat. The procedure was to use rats 185 days old, presumably satiated in all drives except the one being tested. First, the animals were familiarized with the goal object and a standard electric shock; then they were placed in the starting chamber, and the number of approaches, contacts and crossings of the grid were recorded in a 20-min. period. After each crossing, the animal was allowed brief exposure to the goal object and was returned to the starting chamber before any significant amount of consummation. In different experiments, the goal objects were food, water, a receptive female, a male, another rat of the same sex, a litter of infant rats, a new area to be explored or, as a control, an empty, familiar goal box. Thus, it was possible to measure the relative strength of different drives against the standard of the electrified grid as a function of such things as amount of deprivation, degree of deficit or hormonal change in the internal environment, and the type of goal object.

A summary of the major results obtained with this method is shown in figure 3. In terms of the number of crossings of the grid in a 20-min. period, the rank order of drives from the strongest to the weakest is: maternal, thirst, hunger, sex and exploratory. This ordering may only be taken as suggestive, however,

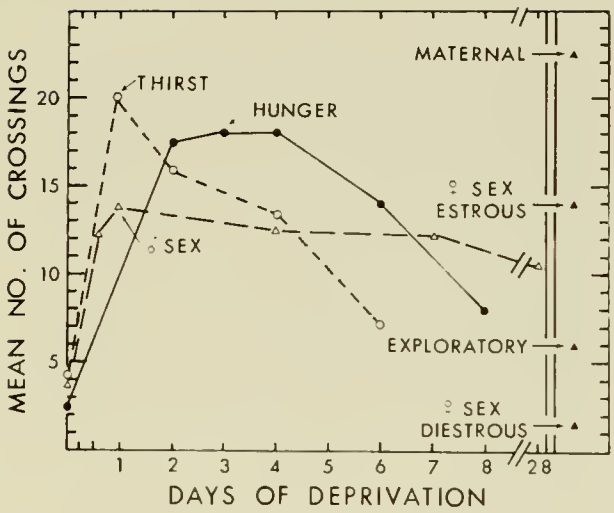



FIG. 3. A summary of obstruction-box data from the rat showing the mean number of crossings of an electrified grid in a 20-min. period to reach different goal-objects. The *abscissa* shows the periods of deprivation of food and water for both sexes and of sexual experience for male rats. *Points* at the *extreme right* show the mean number of crossings made by estrous and diestrous female rats and by multiparous females as well as by rats of both sexes when the goal object was a new compartment that could be explored. [From Warden (164).]

since there was considerable variability in the scores of individual animals, and there is some question as to whether all the conditions of testing were truly comparable.

In addition to this rank ordering, several other findings are worthy of note. In sexual behavior of the female rat, there is a clear association between the frequency of grid crossing and the estrous cycle, the maximum occurring during estrus and the minimum in diestrus, just as in the case of the activity measure. In contrast, the male shows a constant daily rate of crossing, even after varying amounts of sexual deprivation from 12 hr. to 28 days. In the cases of hunger and thirst, on the other hand, as deprivation proceeds, there is a surprisingly early point when the amount of drive decreases. After 1 to 2 days of thirst and 2 to 4 days of hunger, grid crossing decreases in frequency. Perhaps this decrease actually represents a true measure of one aspect of motivation, different from that in the activity and ingestion measures. While we have no experimental evidence illuminating these differences, the obstruction method, nevertheless, is a valuable standard test for the measurement of motivation.

*Choice, Preference and Competition Among Drives*

As pointed out earlier in connection with thirst, much of the strength of motivation is determined by the competition among different drives and the choice among alternative goals. As animals become partly satiated in one motivation, other motivations become prepotent and contribute, by competitive interference, to the decrement of the measured drive. These relationships are seen most clearly in situations where two drives are pitted against each other. The obstruction box, of course, is a commonly used method for the study of competition between hunger, thirst, etc., and pain avoidance. Similarly, experiments have been done where animals are shocked upon eating in order to determine the amount of shock necessary to inhibit eating (98). Or, in other cases, food or water have been adulterated by quinine or some other substance with aversive properties to determine the interference necessary to reduce ingestion or abolish it completely (100). A few attempts have been made to develop tests to compare the strength of different drives by the direct choice method. In one test, the rat is given the choice between going in one direction to a food goal and another direction to a sexual partner (110). In another test, it is determined how much shock has to be delivered to a rat to make it leave a grid and enter cold water, or how cold water has to be to make the rat enter the electrified grid (110).

Several different kinds of methods have been used to study specific hungers and food preferences. The classical method developed by Richter (129) allows the animal to drink from two bottles, one containing water and the other some test solution. The rats have access to the bottles for 24 hr. with food ad libitum, and then, to evaluate position habits and solution preference, the bottles are switched from one side to the other. Thus, an average of 2 days of ingestion gives the preference for the substance tested. For example, the normal rat may take roughly 15 cc from each bottle if both contain water, but it will take 80 to 100 cc from one containing 10 per cent glucose and practically nothing from the one containing water.

Preference may also be measured by the single-stimulus method (20, 166) in which a different solution is given for a 1-hr. period on each day of testing after 15 hr. of water deprivation. Food is not available during the test but is given later in the day in a 5-hr. maintenance period along with plain water. This method has the disadvantage of introducing a constant factor of thirst in the study of specific hunger, but it has two great advantages: *a)* it makes continuous records at the time-course of ingestion quite feasible, and *b)* it makes it possible to test the effects of short-term physiological variables on preference, like the effects of drugs, intubation, etc. In the single-stimulus method, the measure of preference is simply the relative amount ingested, as opposed to the two-bottle method where choice as well as ingestion make up the preference.

Choice is even more important in the two-bottle test where two test substances are offered simultaneously (154). In this test, animals may drink almost exclusively solutions which they can ingest in only small amounts (30 per cent glucose) in preference to solutions they can ingest in large amounts (10 per cent glucose). Thus, preference indicated by choice and by ingestion do not always agree.

The differences among the four methods may be illustrated by the rat's preference for sugar. In Richter's two-bottle method, 10 per cent glucose is the most preferred, for that is ingested in the largest quantity over water (131). In the one-bottle test, where thirst is a factor, 5 per cent glucose is the most preferred (95). Where two sugars are presented simultaneously, 30 per cent glucose is taken in preference to all other solutions (154). Finally, in Young's situation, where ingestion is not a factor at all, the peak preference is for the most hypertonic solutions (173). Obviously, in assessing food preferences it is necessary to make the distinction between how much an animal can ingest and what it chooses.

*Learning and Learned Performance*

While it might be expected that the rate at which an animal learns a new response should be a function of its motivation, it actually turns out that rate of learning is a poor measure of motivation. The rate at which an animal reaches the asymptote of learning is roughly the same over a wide range of strengths of drive and over a wide range of incentives (171). The performance of a learned response, however, is greatly affected by motivation in that the latency of the new response, the number of errors an animal makes, etc., at the asymptote of learning are higher with weak motivation and poor incentives than with strong motivation and highly effective incentives. Thus, it has been shown in a number of studies that performance is affected but rate of learning unchanged with variations in degree of hunger (49), the kind of reward (54), the amount of reward (174) and the number of items of reward with amount held constant (45).

The value of the learning technique in the study of motivation, then, lies primarily in the fact that it offers a large variety of ways of measuring performance as a function of motivation where investigations may be made of such variables as the amount of work required, the amount of ingestion or consummation, the nature of the punishment or reward used as incentive or reinforcement, and the strength of drive varied by deprivation, hormonal changes, etc. Thus, an animal learns to press a lever to get food and its rate of pressing or performance, once it has learned, is a function of its hunger, what kind of reinforcement or reward it gets from pressing, and the amount of work required for each reinforcement (143). For example, the marmoset will perform at a high rate of responding when 10 per cent glucose is given as a reinforcement for every lever-pressing and will hardly work at all for a 40 per cent reward. On the other hand, when 80 lever-pressings are required for each reinforcement, the animal will not work for 10 per cent glucose but will give the highest rate of responding for 40 per cent (unpublished observations). Similar measures of motivation may be obtained from the latency, strength and frequency of response in such learned performances as running down a runway to reach a goal box containing an incentive, lifting the lid of a food cup, jumping from a platform through a window to a goal platform, turning a wheel to get food or getting off a grid that is electrified or can be electrified, etc.

### *Summary*

It is possible, then, to define many of the concepts in motivation operationally and to measure drive, goal-directed behavior and satiation quantitatively. Gross bodily activity yields a measure of undirected drive. Directed drive is measured by strength of consummatory behavior, preference or choice and learned performance (including the obstruction method) as shown by the latency, frequency, speed and magnitude of response. Where goal-directed behavior is involved, it is possible, furthermore, to assess the incentive value of goals, their role in orienting and directing the execution of motivated behavior and their function as rewards and punishments. In all of these cases, satiation may be measured as drive reduction and the competitive interference of other motivation with the expression of the motive being measured.

Drive can be produced by deprivation, deficit, hormonal changes and certain other fluctuations in the internal environment as well as by goal stimuli functioning as incentives. The greater the drive, the greater the activity, the greater the consummatory response, the greater the energy expended and the work done, the greater the barrier that will be overcome to reach a goal, the greater the preference, and the greater the level of learning reached. Increasing drive beyond a certain point, however, may result in a decrement in motivated behavior, in some cases, presumably as a result of physical impairment of the animal. But whether the decrement shows up or not, and at what intensity of drive, will depend upon the measure of motivation used.

## THE NEUROPHYSIOLOGY OF MOTIVATION

In reviewing the literature on the physiological mechanisms underlying motivated behavior, we shall use as a framework the general multifactor mechanism schematically described earlier in this chapter. While this approach loses some of the advantage of discussing each kind of motivation separately, it allows us to focus directly upon the physiological problem, to make useful comparisons among the various kinds of motivated behavior and to point up sharply the gaps in our knowledge of physiological mechanisms. [For a separate discussion of the major kinds of biological motivation see Morgan & Stellar (109).] To be sure, we shall eventually learn that each kind of motivation has its own, unique physiological mechanism; but at this stage of knowledge, the similarities brought out by a unified approach are more important than the differences, for what we can learn about one kind of motivation can be most helpful in our understanding of other kinds.

### *Diencephalic Mechanisms*

The evidence to date strongly points to a major focus of the physiological mechanism in control of motivated behavior in the diencephalon, primarily the hypothalamus. (This is considered in Chapter XXXVII of this work by Ingram.) Physiological studies of this region of the brain implicate it as an important integrating mechanism in the control of autonomic and somatic adjustments of the kind that are important in motivation. For example, Hess (70; cf. 61), in his extensive stimulations of the diencephalon of waking cats with chronically implanted electrodes, was able to produce: changes in arterial pressure, respiration and pupil size; salivation, vomit-

ing, micturition and a normal pattern of defecation, including crouching and covering; a normal sequence of responses leading to and including sleep; rage and defensive reactions, flight and changes in feeding. While some of these responses may be produced upon stimulation of other parts of the central nervous system, the importance of the diencephalon is striking.

While Hess has emphasized the view that functional areas of the diencephalon overlap and thus are poorly localized, the investigations of others offer evidence for much more discrete localization of function. Two general conclusions seem clear from these studies. *a*) There are discrete regions within the hypothalamus where marked changes can be experimentally produced in different types of motivated behavior. *b*) Some of these regions are excitatory in that they yield increases in motivated behavior upon stimulation and decreases in motivated behavior upon ablation; others, by the same criteria, are inhibitory.

Both excitatory and inhibitory regions are found in studies of hunger and sleep. In hunger, bilateral lesions in the vicinity of the ventromedial nucleus of the hypothalamus produce marked hyperphagia, a doubling or a tripling of food intake (30); similar lesions more lateral in the lateral hypothalamus result in starvation (2, 157). Confirmation of the conclusion that the medial region is inhibitory and the lateral excitatory is brought by the fact that stimulation of the medial region through chronically implanted electrodes in the rat markedly depresses food intake whereas lateral stimulation elevates it significantly (85, 145). (See Brobeck's presentation of this matter in Chapter XLVII of this work.) In the case of sleep, discrete bilateral lesions in the posterior hypothalamus in the region of the mammillary bodies cause somnolence (112, 121) while anterior hypothalamic lesions in the preoptic region yield persistent wakefulness (112). Thus, there is a posterior excitatory mechanism and an anterior inhibitory mechanism for wakefulness. Stimulation studies so far have revealed successful induction of sleep only when electrodes are located in the massa intermedia of the thalamus (70), suggesting an additional inhibitory area or another route for reaching the inhibitory mechanism physiologically.[2] (This subject is also discussed by Lindsley in Chapter LXIV of this *Handbook*.)

Several additional points of interest have come from further studies of these excitatory and inhibitory mechanisms. *a*) In both sleep and hunger, the attempt has been made to ablate the excitatory and inhibitory regions in one preparation (2, 112); the result in each case was that the symptoms were the same as those produced by destruction of the excitatory mechanism alone, namely somnolence and starvation. These findings have suggested the possibility that the main influence of the inhibitory area is upon the excitatory mechanism, but they do not rule out the possibility that both the excitatory and inhibitory mechanisms function through a common structure below the diencephalon. *b*) The hyperphagia produced by ventromedial hypothalamic lesions is permanent whereas there is recovery from the starvation produced by lateral lesions if the animals are maintained for several weeks by forced feeding (157). In the case of somnolence following posterior hypothalamic lesions, there is also recovery, with some capacity to maintain wakefulness returning gradually over a period of several weeks (121). These findings suggest additional mechanisms for maintaining wakefulness and feeding behavior.

So far only an excitatory mechanism has been revealed in the study of thirst. Stimulating the diencephalon of the goat electrically or with minute quantities of hypertonic saline directly injected through an implanted pipette will promptly produce great drinking in water-satiated goats (3, 4, 5). The critical area is dorsal to the infundibulum between the fornix and the mammillothalamic tract, just lateral to the paraventricular nucleus, midway between the dorsal and ventral hypothalamus. Similar results have been reported in two investigations using the rat (63, 105). In addition, ablation of the same area in the dog produced adipsia from which there was recovery after 14 days (6).

In the case of sexual behavior, bilateral lesions in the ventral portion of the anterior hypothalamus between the optic chiasm and the stalk of the pituitary will abolish sexual behavior in the female guinea pig, even following the injection of gonadal hormones (35, 52). Similar data have been reported on the male guinea pig (34) and on rats of both sexes (42). Furthermore, upon stimulation of the lateral preoptic area in male and female rats by injection of minute amounts of appropriate sex hormones through an implanted pipette, long-lasting sexual behavior was elicited (56). Thus, there is evidence for an excitatory mechanism for sexual behavior in the hypo-

[2] It is interesting to note, however, that stimulation of the medial reticular formation in the lower medulla of the cat will elicit the postural adjustments of sleep without any sign that the animal is actually asleep (147). Thus it seems possible to separate the response mechanism from the mechanism mediating the arousal and satiation of motivated behavior in experimental procedures of this sort.

thalamus. (See also Sawyer's account of this topic in Chapter XLIX of this *Handbook.*)

The role of the hypothalamus has been less extensively investigated in other kinds of motivation, but the findings available are quite suggestive. Increased emotionality in cats has been demonstrated following lesions in the vicinity of the ventromedial nucleus of the hypothalamus (167), suggesting an inhibitory mechanism. Posterior hypothalamic lesions result in reduced emotionality and placidity (121) and stimulation of these posterior regions produces many of the signs of rage (70, 123), suggesting an excitatory mechanism. Strong and persistent maternal behavior has been elicited in both male and female rats by injection of male and female sex hormones respectively into the medial preoptic area (56). Reductions of gross bodily activity have been reported following lesions near the ventromedial hypothalamus of the rat, even without concomitant hyperphagia (71).

Lacking in all of these experiments, unfortunately, is any precise anatomical work specifying precisely what structures must be involved to give these various effects on motivated behavior. It is not clear in either the ablation or the stimulation studies whether it is cell bodies or fiber tracts or both that must be destroyed or stimulated. The most we can say is that the lesion or the tip of the stimulating electrode or pipette must be in a particular region of the brain to yield significant effects on the particular kind of motivated behavior that is measured.

A further criticism of many studies is that only one kind of motivated behavior is measured upon stimulation or ablation of a particular locus. The physiological studies by Hess show a great deal of overlapping and intermingling of points as far as the kinds of effects he found upon stimulation are concerned. It has also been found that lesions in the vicinity of the ventromedial hypothalamus, designed to produce hyperphagia, will also produce hypoactivity in some rats and emotionality in others. But examination for these additional effects has only been casual in most studies, and we know nothing about whether such lesions would also produce noteworthy changes in sexual behavior, pain avoidance, etc. A number of studies give some idea of the multiplicity of functions that can be revealed from experimentation with one locus. For example, lateral hypothalamic lesions eliminate hunger and thirst simultaneously and often produce transient somnolence (157). In his experiments, Fisher (56) found that injection of sex hormones into the anterior hypothalamus could elicit maternal and sexual behavior simultaneously, and in addition could sometimes produce changes in respiration, exploratory behavior, digging, leaping, etc.

Thus, only the crudest questions about localization of function within the diencephalon can be answered on the basis of the present data on motivated behavior. At present, it appears that there are different foci in the diencephalon which can be manipulated experimentally by stimulation and ablation to produce marked changes in different kinds of motivated behavior. Some of these foci can be characterized as excitatory and others as inhibitory. But much more has to be done experimentally, on the anatomical side and on the behavioral side, before we can conclude much beyond these two points.

### *Other Central Mechanisms*

Investigation of other central neural structures outside the diencephalon has revealed much about their role in motivation. Again, it is possible to characterize the function of many of these regions of the brain as excitatory or inhibitory in terms of the effects of lesions and stimulations on the arousal and satiation of motivated behavior. Perhaps the most thoroughly studied kind of motivation is emotional behavior, although the picture we have at present is not entirely clear. (Its present status is considered in Chapter LXIII by Brady in this work.) Decortication, as Bard showed, leads to 'sham rage,' suggesting an inhibitory role of the cortex in emotion (8); while Bard & Mountcastle (9) found that ablation of parts of the rhinencephalon, particularly the amygdala and transitional cortex of the mid-line, produced great increase in the ferocity of cats. Removing only the neocortex, on the other hand, resulted in extremely placid cats. In other studies on monkeys and cats, rhinencephalic ablations, including parts of the tip of the temporal lobe and the hippocampus in some cases, led to placidity rather than ferocity (81, 135). So far this disagreement is unresolved, but it is clear that certain parts of the cortex may exert an inhibitory effect and others an excitatory effect on emotional behavior.

Contributions from other parts of the brain to emotional behavior have been revealed in a number of other studies. *a*) An inhibitory role is suggested for the septal area where lesions produce a transient, but greatly exaggerated, emotional response to tactile stimuli in rats (27). *b*) There is evidence for an excitatory contribution from the brain-stem reticular system and mid-line thalamic nuclei (76, 91, 92). *c*) There is an inhibitory contribution from the anterior nuclear complex of the thalamus, ablation of which causes

cats to solicit petting and respond to it with heightened 'pleasurable' reactions (137). *d)* There have been reports of reduced emotionality following cingulectomy (119, 120) and the frontal lobes have been implicated, although their contribution is not entirely clear (59).

The situation is somewhat clearer in the case of sexual behavior. Here it has been found that neocortical lesions lead to a reduction in sexual motivation, the larger the lesion in the male rat the greater the effect without regard to locus (12); females are less affected than males by cortical ablations; and the higher the animal on the mammalian scale, the greater the effect (15, 17). In addition to this excitatory role of the neocortex, there is evidence for an inhibitory role of the amygdala (135, 136) and overlying pyriform cortex (43), in male cats at least. After some delay following ablation of these regions, there may be exaggerated sexual responses in male cats and monkeys characterized by strong drive and poor discrimination of sexual objects. (See also Chapter XLIX on reproductive behavior and Chapters LVI, LVII and LVIII on the limbic system in this *Handbook*.)

In the case of sleep, it has been found that decortication in dogs is followed by an inability to postpone sleep and maintain wakefulness for long periods of time with the result that such dogs sleep and wake in short cycles over the 24-hr. period (80). Similar excitatory contributions are revealed in human cases with restricted cortical and thalamic lesions (46–48). Most striking of all, however, is the excitatory contribution from the brain-stem reticular formation (91, 92). Lesions here are followed by marked somnolence, and central stimulation leads to prompt arousal from sleep.

Little is known about the role of central neural structures outside the diencephalon in hunger and thirst, although overeating has sometimes been reported as a result of frontal lobe damage (132, 133). In maternal behavior and in food-hoarding, it has been reported that destruction of mid-line cortex in the rat leads to a reduction in motivation as well as a disintegration of the organization of these patterns of behavior (148, 149). Finally, some suggestion about an excitatory role of the frontal cortex in the motivation to avoid pain comes from the psychosurgical studies done for the relief of intractable pain (57). In these cases, the patients report postoperatively that while they still feel the pain, it no longer bothers them as before.

Because of the lack of good anatomical data relevant to these problems, it is impossible to say definitely by what route these structures exert their excitatory and inhibitory effects on motivated behavior. The most common hypothesis is that they work through the integrating mechanisms of the hypothalamus, for many pathways to this structure have been described. Thus it has been suggested that the contribution of the rhinencephalic cortex to emotional behavior is mediated by the amygdala which in turn functions through the ventromedial nuclei of the hypothalamus (9). While such hypotheses are reasonable in the light of a concept of hierarchical organization of the central nervous system and are part of the theoretical viewpoint followed here, it will remain for future experimental work to supply the detailed evidence needed for their support. For example, although we may conclude clearly that a part of the cortex has an excitatory or an inhibitory effect on motivated behavior, we do not know whether its physiological role is excitatory or inhibitory, for under the present viewpoint, it may exert its influence on either an excitatory or inhibitory diencephalic mechanism, or have a reciprocal influence on both. Or by alternative anatomical and physiological routes, it may bypass these mechanisms.

### *Sensory Factors*

From both anatomical and physiological evidence, it is quite clear that the hypothalamus is under extensive sensory control, receiving afferents directly from all the modalities over the specific pathways and, through collaterals, over the nonspecific pathways of the reticular system (60, 90, 151). Furthermore, on the basis of extensive behavioral evidence, a primary role must be given to sensory factors in the control of motivated behavior. It has already been pointed out that mammalian sexual motivation may be destroyed by peripheral surgical reduction or elimination of two or more sensory avenues (16). In this case, the sensory contribution to arousal is nonspecific since any one sensory path can be eliminated without significant effect. In his analysis of sleep, Kleitman (79) draws the similar conclusion that it is the sum total of afferent input that controls wakefulness rather than any specific sensory system, and this notion is inherent in Magoun's conception (92) of the role of the brain-stem reticular formation. Direct support for these views comes from Bremer's preparations in which waking EEG patterns survive brain section until there is a sufficient reduction in afferent input (28, 29).

Our knowledge of hunger and thirst suggests that the arousal of motivated behavior in these cases should be a joint function of sensory impulses arising from gastric contractions or dryness of the throat, and taste, tactile and temperature receptors in the mouth. There are no sensory deprivation experiments to provide a good test of this point, but everything we know about the acceptability of foods and fluids of different temperatures, consistencies and flavoring suggests the joint operation of many stimuli in the control of these types of motivation.

In addition to sensory contributions leading to the arousal of motivated behavior, it is clear that some stimuli can be inhibitory and lead to the reduction of motivation. Most striking are the so-called aversive taste stimuli like quinine which are strong enough to inhibit eating or drinking (100). In hunger and thirst, there also seems to be an inhibitory sensory effect arising from the stomach, judging from the effects of loading food and fluids into the stomach and mechanically stretching it (1, 75, 106, 153). Furthermore, the fact that animals with esophageal fistulas stop eating and drinking at some point even though nothing enters the stomach (21, 140, 153) suggests that the stimuli that feed back from consummatory behavior might have a net inhibitory effect on hunger and thirst.

Many other studies shed light on the role of sensory factors in motivation. Some of these we will discuss below when we take up the interaction of factors controlling motivation. Others we must omit because at the present stage of knowledge, we have no idea through what neurophysiological mechanism they act. What is needed, obviously, is direct experimental evidence on the relation between peripheral sensory factors and central neural mechanisms. A start has been made in the finding that changes in the electrical activity of the lateral part of the anterior hypothalamus may be induced by vaginal stimulation of the estrual cat (118). But until we have more information of this sort, any specific notions about the mechanisms whereby excitatory and inhibitory sensory contributions are made to the arousal and satiation of motivation must remain rather speculative.

### *Internal Environment Factors*

Because the hypothalamus is highly vascularized (44) and borders on the third ventricle, it has been strongly suspected in the past that it may be a major site of interaction between the internal environment and the nervous system. Fortunately, we now have some direct information on this point in the study of motivated behavior. One striking line of investigation, already mentioned, involves the direct introduction of substances into the brain in an effort to imitate experimentally the role of the internal environment in motivation. Minute quantities of sex hormones or hypertonic solutions that would be totally ineffective if introduced systemically can produce marked and persistent changes in motivated behavior when introduced directly into the hypothalamus through chronically implanted pipettes. Out of this and related work has grown the notion that there are special 'receptor' cells in the central nervous system, selectively sensitive to certain chemicals or hormones or physical changes in the blood and cerebrospinal fluid. Thus, it has been suggested that there are temperature (31) and glucostatic receptors (93, 94) important in hunger, osmoreceptors (3, 160) critical in thirst, temperature receptors (122) playing a role in body temperature regulations and perhaps motivated behavior related to it, and possibly hypothalamic cells especially sensitive to such drugs as amphetamine (32), an appetite depressant.

The evidence from direct injections is not entirely clear at this point, however. Preliminary results have shown that sex hormones arouse sexual behavior, but they also arouse maternal behavior, changes in respiration, exploration and digging. In the case of thirst, the evidence for osmoreceptors derives from the fact that hypertonic solutions arouse drinking and water does not. As Larsson has shown, however, hypertonic solutions will also elicit eating, rumination, chewing and licking in goats when injected into other parts of the hypothalamus (85). Perhaps these solutions have rather widespread or general stimulating effects similar to those of electrical stimulation. Thus, while the present evidence is suggestive, it is by no means conclusive.

There is, however, much additional evidence to support the general notion that the hypothalamus is critical in the mediation of the effects of the internal environment on motivated behavior. In the case of sexual behavior in the ovariectomized female cat (33) and in the guinea pig (51), for example, section of the nervous system below the hypothalamus made the contribution of sex hormones ineffective in the elicitation of estrual behavior by sacral and vaginal stimulation. If the hypothalamus were included below the section, however, sex hormones were effective in rendering the response mechanisms reactive to stimulation. Supporting the conclusion that the site of action of the sex hormones may be in the hypothalamus is

the fact that sex hormones are ineffective following discrete lesions in the ventral hypothalamus just anterior to the pituitary stalk (35).

In one striking case, it has been shown that amphetamine, an appetite depressant, selectively activates the ventromedial hypothalamus in the anesthetized cat (32). While this finding suggests that the site of action of amphetamine may be the hypothalamus, it seems clear that this cannot be the sole site of action since amphetamine can still depress the appetite of the rat after bilateral ablation of the ventromedial hypothalamus (155).

Finally, we have the excellent example of specificity of hormonal action on the nervous system in the work of Bonvallet *et al.* (24). They showed that epinephrine had its effects on restricted loci in the mesencephalon in its activation of the waking EEG pattern, and in the facilitation and inhibition of spinal reflexes.

Results such as these make it most interesting to ask about the mechanisms and sites of action of other internal environmental changes that are known to be important in motivation. How does insulin affect the nervous system to produce its enhancement of hunger; how does the salt deficiency of the adrenalectomized rat lead to salt hunger, thiamin deficiency to thiamin hunger; etc.? It seems unlikely that there are separate 'receptors' in the hypothalamus for each of these chemical and physical changes in the internal environment. It is possible that there are a limited number of overlapping mechanisms sensitive to internal changes and that such specificity as does occur in the selective arousal of motivated behavior might be the joint outcome of a particular combination of internal and sensory variables.

### *Interaction of Factors*

It is quite obvious from the foregoing that it is as important to understand the joint action of the various factors contributing to the multifactor control of motivation as it is to know their individual influences. A number of studies approach this question of the interaction of factors. The problem is well illustrated in the case of specific hungers for solutions of sodium chloride, glucose and saccharin (20, 95, 153, 166). In all three of these cases, the ingestion of the solution increases as a function of the concentration up to a certain point and then decreases (fig. 4). This lawful pattern of ingestion is determined by a number of factors operating together. *a)* Some of the drinking, particularly at the lower concentrations, is produced by dehydration since water deprivation or hypertonic saline injection will increase the ingestion of the weak concentrations (95, 153). *b)* The increasing intake as a function of concentration over the lower ranges seems to be a result of increasing intensity of taste stimulation, for in the case of sodium chloride, it quite clearly parallels the increasing discharge of the chorda tympani in response to increasing concentrations of sodium chloride solutions (115). And in the case of saccharin, the only thing known to vary with concentration is taste. *c)* The decreasing ingestion in the higher ranges of concentration seems to be produced by two factors. One is a second sensory factor, a negative taste factor (bitter) in saccharin and possibly pain in sodium chloride ingestion. A second factor is a consequence of the ingestion of hypertonic solutions, namely dehydration. The separation of the negative taste factor and the dehydration factor is seen in the ingestion of salt solution by rats with esophageal fistulas (153). These animals take decreasing amounts of higher and higher concentrations of sodium chloride, suggesting a negative sensory factor, but the drop-off with increasing concentration is nowhere near as rapid as it is in the normal animal. Secondly, the animal with a fistula does not reduce its intake of hypertonic saline following water deprivation but rather increases it, emphasizing the role of postingestion dehydration. *d)* Finally, in the case of salt hunger at least, the internal environment is important, for as it is increasingly depleted of salt following adrenalectomy, the ingestion of salt solutions of all concentrations increases (10, 55).

Other instances of the joint operation of several variables in the control of motivated behavior have not been as completely worked out but are of interest because they provide more information on the central neural mechanism. Beach's report (12) of the restoration, by sex hormone injection, of sexual motivation lost through cortical lesions is one good example. Another is the report of Brooks (36) that neither decortication nor olfactory bulb ablation in the male rabbit eliminates sexual behavior, but a combination of the two does. A third is the report of Schreiner & Kling (136) that castration destroys the hypersexuality induced in male cats by amygdalectomy.

Perhaps one of the better studies showing the joint contribution of two or more factors to the control of motivated behavior is the work of Teitelbaum (156) who investigated the changes in the sensory control of eating produced by ventromedial hypothalamic lesions. He found that hyperphagic rats reject powdered laboratory food, adulterated with nonnutritive

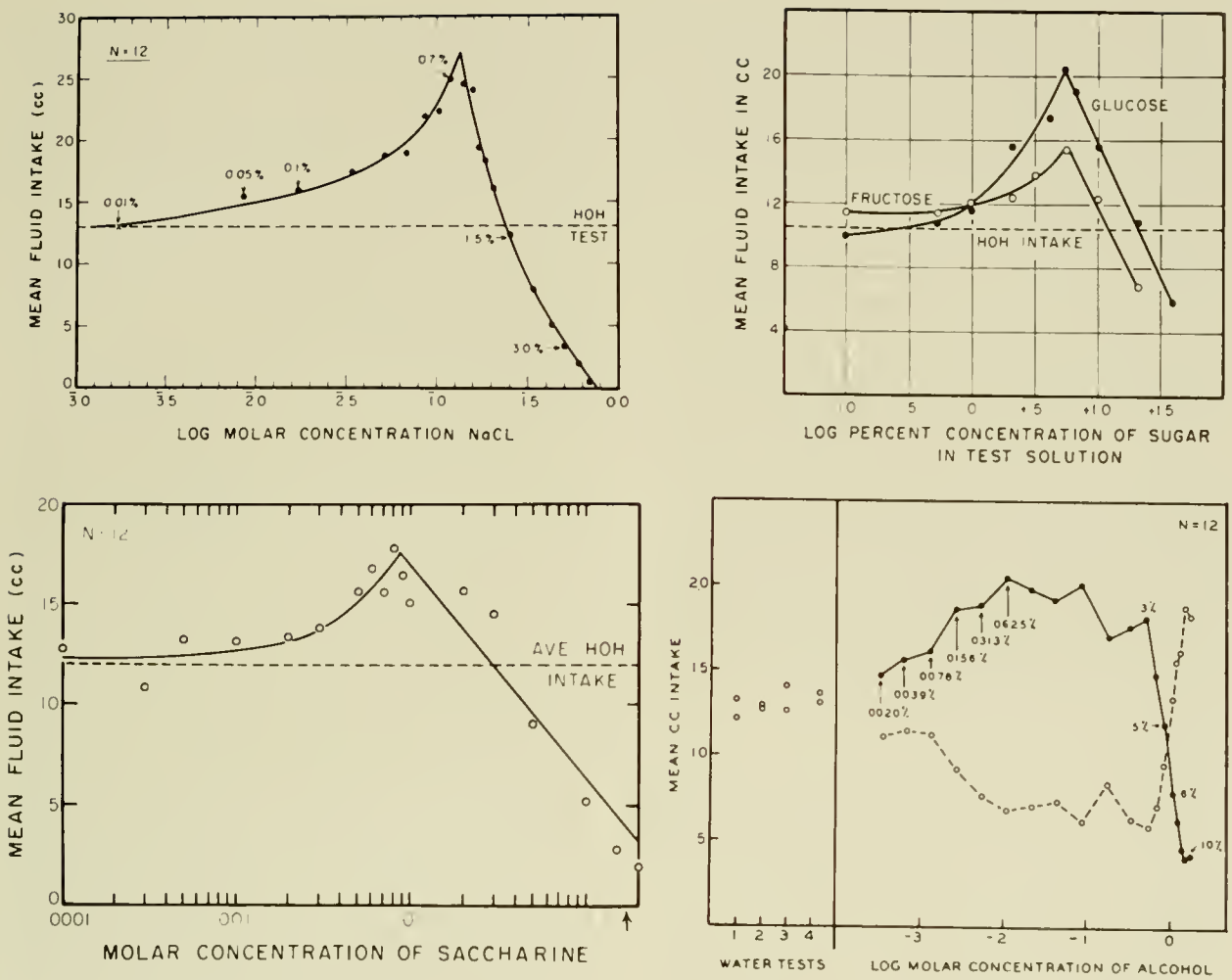



FIG. 4. Preference-aversion curves for different foods offered in solution, showing fluid intake as a function of the concentration of the solution. The sodium chloride, the glucose and fructose, and the saccharin functions are based upon 1 hr. of drinking in the single stimulus method; the alcohol function is based on 24 hr. drinking of alcohol and water in the two-bottle method. [The sodium chloride data are from Stellar *et al.* (153); the sugar data, from McCleary (95); the saccharin and alcohol data, from Stellar, unpublished observations.]

cellulose, at much lower percentages of adulteration than normal rats. This result suggested the importance of changes in the operated animal's reactivity to the sensory stimuli provided by the diet, possibly even in the original overeating of regular laboratory food. This hypothesis was, in part, confirmed by the finding that hyperphagic rats ingest more of the powdered diet when 50 per cent glucose is mixed with it, and less when a low concentration of quinine is added or when the food previously given in the form of pellets is presented in powdered form—neither of which changes influence the intake of normal rats. Thus, whether a lesion of the ventromedial hypothalamus leads to overeating or undereating, relative to normal, is a function of the nature of the sensory stimuli provided by the diet.

Two additional results are of note here. *a*) Rejection of cellulose-adulterated food was also observed in rats with similar lesions that did not become hyperphagic, suggesting the possibility that the refusal to eat certain foods might be dependent upon structures outside of the inhibitory feeding mechanism in the ventromedial hypothalamus. *b*) Hyperphagic rats that are not allowed to become obese do not respond

abnormally to the addition of quinine and glucose to the diet or to the change in texture. But they are sensitive to cellulose adulteration. It is possible, then, that obesity makes some indirect contribution to the 'finickiness' Teitelbaum reports, although this finding may be partly the result of the 'heedless' eating the nonobese hyperphagics do.

In similar studies, rats with lateral hypothalamic lesions accept no food postoperatively. But as recovery occurs, on a regime of forced feeding, it comes about in a very specific way. After a week or two of complete starvation, the operated rats will accept chocolate and evaporated milk, but they cannot be aroused to drink water or eat powdered food, glucose, meat, etc. Within a few days to a few weeks later, they will accept water and, last of all, they will eat powdered food. While there are undoubtedly many chemical and nutritive differences among these substances in addition to sensory ones, the suggestion is strong that these rats are changed in their reactions to the stimuli provided by the diet following operation and throughout the course of recovery.

### *The Role of Learning*

Our discussion of the physiological mechanisms of motivation would not be complete without consideration of the role of learning. Unfortunately, we are hampered in our thinking by our ignorance of the physiology of learning, but there are experiments on motivation, involving learning, which are particularly instructive at the behavioral level and give us some valuable ideas about the general nature of the underlying mechanisms. Three different kinds of experiments are of interest here: *a*) studies of the influence of learning in the modification of biologically adaptive motivated behavior; *b*) comparisons of the effects of a number of physiological variables on motivation in which learned performance as opposed to unlearned consummatory response is used as the measure of motivation; and *c*) direct physiological studies of reward and punishment, and the reinforcement of learning and learned performance.

Illustrative of the first kind of study is the postoperative ingestion of sodium chloride by the adrenalectomized rat. Epstein & Stellar (55) have shown that the rat requires no special postoperative experience to increase its sodium chloride intake following adrenalectomy. On the other hand, Harriman (66) has demonstrated that rats given experience with glucose and sodium chloride solutions before operation, unlike naive rats, will prefer glucose to sodium chloride postoperatively and will die because they fail to ingest sufficient amounts of salt. In a similar type of experiment, Young (172) has shown that protein-deficient rats will prefer sucrose to protein in a test situation where they had been in the habit of selecting sucrose before any deprivation; if placed in a new test situation, however, where they have no previous habits, they show an immediate preference for protein; if tested in the two situations on alternate trials, they alternate between sugar and protein preference. Similar interfering and facilitating effects of previous habits have been shown in many other studies (67, 138, 139), and they hint at how complicated the mechanism of motivation can become when the opportunity for learning is introduced. This problem has been solved in most of the experiments we have discussed so far by keeping the possibilities of learning at a minimum by using as a measure of motivation a simple, uncomplicated consummatory response, natural to the animal. But as you will see in a moment, this may be a misleading practice, and our conclusions about the physiology of motivation should properly be based on measures of learned performance as well as consummatory measures.

A number of experiments have been done comparing results with the measure of learned performance and the consummatory response. In a striking study of rats with lesions of the ventromedial hypothalamus, Miller *et al.* (102) were able to show that while hyperphagic rats ate more than normals in a free-feeding situation, they showed much less hunger motivation than normals when required to perform learned responses, to work or to overcome the taste of quinine to get food. In the face of these contradictory findings, the authors suggest that ventromedial lesions may not release hunger motivation for easier arousal but simply interfere with the mechanism for stopping eating. However, it is well to point out that the hyperphagics used in this study were obese and, judging from Teitelbaum's findings cited above, the results reported here may be as much a matter of obesity as they are of hypothalamic lesions.

In a series of different experiments by Miller and his students (22, 82, 101, 103, 104), much better agreement was found between the consummatory measure and the learned-response measure. In these studies, they used rats with gastric fistulas so that they could compare the effects of saline, milk or water introduced directly into the stomach or taken by mouth. Using both hungry and thirsty rats, they found that taking fluid by mouth had greater satiating effects whether they used as a measure of motivation

later consummation or performance of a learned response involving very little consummation. They were also able to show that injection of fluid directly into the stomach could be used as the reward to promote the learning of a simple maze, but that allowing animals to drink milk or water by mouth was an even more effective reward.

In another study, modeled after Andersson's work on the goat, this same laboratory was able to confirm the finding that intraventricular injections of minute quantities of hypertonic solutions increased the thirst of cats, and to demonstrate further that injections of water and hypotonic solutions led to decreased thirst. This result turned up with the use of a consummatory response as a measure and also with the use of a learned response in which the animal worked for relatively few opportunities to drink (101). In similar studies with food, there has been some question as to whether stimulating the medial hypothalamus electrically elicits hunger motivation or merely evokes reflexes of seizing, chewing and swallowing, for stimulated animals sometimes seize and chew nonedible objects. That there is an actual increase in motivation upon stimulation of the ventromedial hypothalamus, however, is confirmed by the fact that following stimulation these animals will press a bar many times to get an occasional tiny bit of food, even though they are otherwise satiated (101).

Obviously, agreement among the various measures of motivation in determining the effects of a physiological variable strengthens the conclusions we can draw about the mechanism of motivation. Disagreement may mean one of two things, however: that there is interference with something specific to the behavior involved in the affected measure, not necessarily of a motivational nature, or that there are different facets of motivation measured by the different tests and subserved by somewhat different physiological mechanisms. Clearly, it will be profitable to extend the measures of motivation used in physiological studies to include techniques that are not solely dependent upon consummation.

The third and most striking kind of experiment involving learning is the use of electrical stimulation of the brain to serve the function of a reinforcement, much like a food reward for a hungry animal, or much in the way that escape or avoidance of an electric shock reinforces a new response. The first study along these lines was by Delgado *et al.* (50). By implanting electrodes in the vicinity of the medial lemniscus and posteroventral nucleus of the thalamus, these workers were able to elicit clear negative motivation in cats of the sort observed upon administering electric shocks to the feet. They reported four major results. *a)* Cats learned to rotate a wheel to turn off this central stimulation. *b)* They learned to respond to an auditory signal by turning the wheel in order to avoid the stimulation that had always followed the signal previously. *c)* They learned to escape immediately when placed in a compartment in which they had received central stimulation. *d)* Central stimulation administered at the time of feeding inhibited eating for long periods of time, despite strong hunger. Thus by stimulation in the vicinity of the pain pathways centrally, these workers were able to elicit strong negative motivation, sufficient to reinforce a variety of kinds of learning.

On the positive reinforcement side, Olds & Milner (114) have reported that rats will work in order to be stimulated at a number of points within the brain. If an electrode is chronically implanted in the septal area or the mamillothalamic tract and activated every time after the rat presses a lever, the animal will change its rate of pressing the lever from several times an hour to as high as almost 750 times an hour. Self-stimulation of the cingulate gives similar but less marked results, while corpus callosum, caudate and hippocampal stimulation yielded no effect. Stimulation of the tegmentum was equivocal, and medial lemniscus and medial geniculate stimulation, if anything, produced avoidance of the lever.

Following this same procedure of self-stimulation reinforcement with rats and cats, Sidman *et al.* (141) used the technique of administering stimulations only after certain lever pressings. When the schedule of stimulations called for activation of the implanted electrode at irregular intervals of time, averaging 16 sec., low rates of responding were obtained. When the schedule called for seven pressings for each stimulation, the rate of responding was very high. These results were typical of those obtained with such variable-interval and fixed-ratio schedules of reinforcement with food or water as the rewards. Thus, it appears that under appropriate experimental conditions, stimulation of the brain can be rewarding and can reinforce the performance of a learned response in much the same manner as food and water do for the hungry or thirsty animal.

In this work, Sidman *et al.* found stimulation of the septal area most effective for the rat and the caudate for the cat. In a later study on the rat, Olds (113) concluded that the stimulation of the amygdaloid complex and the anterior hypothalamus were as effective as stimulation of the septal area in yielding high

rates of responding, while moderate rates were produced upon stimulation of the cingulate, hippocampus, posterior hypothalamus and anterior thalamus. The distinction between effective and ineffective points, and rewarding and punishing points, however, may not be simple. Miller and his colleagues (101) have reported that a single point may be positively reinforcing in the sense that an animal will work to have it stimulated; but it may also be negatively reinforcing, for the animal will escape from it if it has the opportunity.

From a purely behavioral point of view, it looks as though direct stimulation of the brain should have the same physiological effect as the various rewarding consummatory responses that eventually lead to satiation. This notion is supported by the fact that so many of the effective points for self-stimulation reinforcement are in areas of the brain that are known to play an important role in motivation. However, we lack the specific experimental information as yet to tell whether the reinforcing effects are tantamount to transient drive reductions or satiations of specific motivations through appropriate activation of their specific mechanisms; or whether these reinforcing effects are not specific to any of the mechanisms of motivation, but rather evidence for a general mechanism for 'pleasure' or, put more operationally, reinforcement. Preliminary reports on human patients with electrodes implanted in the septal area indicate 'feelings of comfort' upon stimulation (68). But it is too early to speculate beyond these general possibilities, for at present there are too few facts at hand.

## CONCLUSIONS

A number of conclusions can be derived from this historical and experimental analysis of the physiological basis of motivated behavior.

It is possible to study motivated behavior with objective methods and to make an operational analysis of the factors important in its control without resort to teleological and vitalistic concepts.

This analysis indicates that various kinds of motivated behavior, like hunger, specific hungers, thirst, sex, maternal behavior, emotion, sleep, etc., are under the same general kind of multifactor control, receiving influences from the various sensory avenues, the internal environment and the central nervous system.

An often neglected, but nevertheless important factor is learning, for previously neutral stimuli can, through experience, come to contribute to the arousal and satiation of motivated behavior, and various new instrumentalities and goals may be learned in the execution of motivated behavior.

The relative contribution of the various factors controlling motivation and presumably the underlying physiological mechanisms change in the course of phylogeny. Judging mainly from the example of sexual behavior, there is with ascending phylogenetic position an increasing dependence upon sensory factors, learning and the cerebral cortex, and a decreasing dependence upon the internal environment.

The behavioral analysis of motivated behavior divides it into three main aspects: drive, the intensity of the arousal and maintenance of motivation; goal-directed behavior, the enhanced perception of selected stimuli in the environment and the selective execution of a pattern of behavior in respect to them; and satiation, the reduction of drive once the goal is sufficiently attained.

Experimental methods are available to measure drive and satiation quantitatively and to specify, in some cases, the choice and selection involved in goal-directed behavior. The possibilities for the measurement of motivation are greatly increased by the learning of new drives, new goals and new instrumentalities for attaining goals. There are, however, two important limitations in the present methodologies: *a*) the various measures of motivation are not always in good agreement, and *b*) there is too much dependence at present upon simple measures of consummatory response.

Physiologically, drive appears to be a function of the activity of a general excitatory mechanism having its major central control in the hypothalamus, and satiation is a function of a similar inhibitory mechanism, for increases and decreases in many kinds of motivated behavior can be produced by ablation and stimulation of restricted hypothalamic foci. There are two serious limitations in the conclusions we can draw about localization, however. *a*) We do not know, with any anatomical precision, the structures in the hypothalamus which must be involved to produce these changes in motivation; we do not even know whether lesions and stimulations are effective because they affect nuclei or fiber tracts or both. *b*) We do not know whether a particular effective locus subserves only one kind of motivation or several kinds, although there is much evidence suggesting overlap of function within the hypothalamus.

Central neural structures outside of the hypothalamus also contribute excitatory and inhibitory influences to the control of motivation as many ablation

and stimulation studies show. The current hypothesis is that neocortical and rhinencephalic structures exert their influence directly through the hypothalamic integrating mechanism; but we have very little direct evidence on the anatomical and physiological pathways involved.

Analysis of the sensory contribution to the arousal and satiation of motivation shows that it is typically a multisensory matter in which the influence from the various sensory pathways is additive. As yet, however, there is only a small amount of information showing direct sensory contribution to the hypothalamic mechanisms involved in motivation.

The important role of the internal environment in motivated behavior is thought to be mediated largely through the hypothalamus. Particularly relevant are the arousal of motivation by direct injection of substances into the hypothalamus and the failure of systemically injected hormones to elicit motivation following hypothalamic lesions.

The complexity of the neurophysiological mechanisms described here is greatly increased by two facts. *a*) These various influences on the hypothalamic mechanisms interact in the arousal and satiation of motivated behavior in the sense that one kind of influence may add its effects to another. *b*) The possibilities for the arousal, expression and satiation of motivation are greatly expanded by learning, undoubtedly altering the underlying physiological mechanism in some way as yet unknown.

Electrical stimulation of the brain can serve to reinforce learning and learned performance in much the same way that food reinforces the hungry animal. It is too early to speculate about the nature of the mechanism involved here, but it is perhaps significant that many of the reinforcing points within the brain are known to be important parts of the physiological mechanism involved in motivated behavior.

Little has been said and little is known about the mechanism for the execution of motivated behavior. The hypothalamus has been thought of as a major integrating mechanism in the expression of motivation, but not much is known about the spinal and brain-stem reflex mechanisms involved. Some good evidence points to the role of the cortex in the spatial and temporal organization of motivated behavior (151), but space has not permitted discussion of this very important question.

A second neglected problem has to do with perceptual changes in motivated behavior. We have discussed only the relatively nonspecific role of afferent systems in the arousal of motivation, but the motivated organism is highly specific and selective in its perception of the environment, as many ethological and psychological studies show. Unfortunately, we have very little physiological evidence relevant to this problem.

We have made only a start on the elucidation of the physiological mechanisms underlying motivated behavior, but a basic core of knowledge and a general orientation have been established.

## REFERENCES


1. ADOLPH, E. F. *Am. J. Physiol.* 151: 110, 1947.
2. ANAND, B. K. AND J. R. BROBECK. *Yale J. Biol. & Med.* 24: 123, 1951.
3. ANDERSSON, B. *Acta physiol. scandinav.* 28: 188, 1953.
4. ANDERSSON, B. AND S. M. MCCANN. *Acta physiol. scandinav.* 35: 191, 1955.
5. ANDERSSON, B. AND S. M. MCCANN. *Acta physiol. scandinav.* 33: 333, 1955.
6. ANDERSSON, B. AND S. M. MCCANN. *Acta physiol. scandinav.* 35: 312, 1956.
7. BAILEY, P. AND F. W. DAVIS. *Proc. Soc. Exper. Biol. & Med.* 51: 307, 1942.
8. BARD, P. *A. Res. Nerv. & Ment. Dis., Proc.* 19: 190, 1939.
9. BARD, P. AND V. B. MOUNTCASTLE. *A. Res. Nerv. & Ment. Dis., Proc.* 27: 362, 1947.
10. BARE, J. K. *J. Comp. & Physiol. Psychol.* 42: 242, 1949.
11. BASH, K. W. *J. Comp. Psychol.* 28: 109, 1939.
12. BEACH, F. A. *J. Comp. Psychol.* 29: 193, 1940.
13. BEACH, F. A. *Psychosom. Med.* 4: 173, 1942.
14. BEACH, F. A. *Psychol. Bull.* 39: 200, 1942.
15. BEACH, F. A. *Psychosom. Med.* 6: 40, 1944.
16. BEACH, F. A. *Physiol. Rev.* 27: 240, 1947.
17. BEACH, F. A. *Psychol. Rev.* 54: 297, 1947.
18. BEACH, F. A. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951, p. 410.
19. BEACH, F. A. *Psychol. Rev.* 62: 401, 1955.
20. BEEBE-CENTER, J. G., P. BLACK, A. C. HOFFMAN AND M. WADE. *J. Comp. & Physiol. Psychol.* 41: 239, 1948.
21. BELLOWS, R. T. *Am. J. Physiol.* 125: 87, 1939.
22. BERKUN, M. M., M. L. KESSEN AND N. E. MILLER. *J. Comp. & Physiol. Psychol.* 45: 550, 1952.
23. BLOOMFIELD, A. AND M. L. TAINTER. *J. Lab. & Clin. Med.* 28: 1680, 1943.
24. BONVALLET, M., P. DELL AND A. HUGELIN. *J. physiol., Paris* 46: 262, 1954
25. BORING, E. G. *A History of Experimental Psychology*. New York: Appleton, 1929.
26. BOUSFIELD, W. A. AND F. A. MOTE. *J. Exper. Psychol.* 32: 450, 1943.
27. BRADY, J. V. AND W. J. H. NAUTA. *J. Comp. & Physiol. Psychol.* 46: 339, 1953.
28. BREMER, F. *Compt. rend. Soc. de. biol.* 124: 842, 1937.
29. BREMER, F. In: *Brain Mechanisms and Consciousness*, edited by J. F. Delafresnaye. Springfield: Thomas, 1954, p. 137.

30. Brobeck, J. R. *Physiol. Rev.* 26: 541, 1946.
31. Brobeck, J. R. *Yale J. Biol. & Med.* 29: 565, 1957.
32. Brobeck, J. R., S. Larsson and E. Reyes. *J. Physiol.* 132: 358, 1956.
33. Bromiley, R. B. and P. Bard. *Am. J. Physiol.* 129: 318, 1940.
34. Brookhart, J. M. and F. L. Dey. *Am. J. Physiol.* 133: 551, 1941.
35. Brookhart, J. M., F. L. Dey and S. W. Ranson. *Proc. Soc. Exper. Biol. & Med.* 44: 61, 1940.
36. Brooks, C. M. *Am. J. Physiol.* 120: 544, 1937.
37. Browman, L. G. *J. Exper. Zool.* 75: 375, 1937.
38. Browman, L. G. *J. Exper. Zool.* 91: 331, 1942.
39. Browman, L. G. *J. Comp. Psychol.* 36: 33, 1943.
40. Cannon, W. B. *A Handbook of General Experimental Psychology*, edited by C. Murchison. Worcester, Mass.: Clark Univ. Press, 1934, p. 247.
41. Carr, W. J. *J. Comp. & Physiol. Psychol.* 45: 377, 1952.
42. Clark, G. *Am. J. Physiol.* 137: 746, 1942.
43. Clemente, C. D., J. D. Green and J. de Groot. *Anat. Rec.* 127: 279, 1957.
44. Craigie, E. H. *A. Res. Nerv. & Ment. Dis., Proc.* 20: 310, 1940.
45. Crespi, L. P. *Am. J. Psychol.* 55: 467, 1942.
46. Davison, C. and E. L. Demuth. *A. M. A. Arch. Neurol. & Psychiat.* 53: 399, 1945.
47. Davison, C. and E. L. Demuth. *A. M. A. Arch. Neurol. & Psychiat.* 55: 126, 1946.
48. Davison, C. and E. L. Demuth. *A. M. A. Arch. Neurol. & Psychiat.* 55: 364, 1946.
49. Deese, J. and J. A. Carpenter. *J. Exper. Psychol.* 42: 236, 1951.
50. Delgado, J. M. R., W. W. Roberts and N. E. Miller. *Am. J. Physiol.* 179: 587, 1954.
51. Dempsey, E. W. and D. McK. Rioch. *J. Neurophysiol.* 2: 9, 1939.
52. Dey, F. L., C. Fisher, C. M. Berry and S. W. Ranson. *Am. J. Physiol.* 129: 39, 1940.
53. Dunlap, K. *J. Abnorm. & Social Psychol.* 14: 35, 1919–20.
54. Elliott, M. H. *Univ. Calif. (Berkeley) Publ. Psychol.* 4: 19, 1928.
55. Epstein, A. N. and E. Stellar. *J. Comp. & Physiol. Psychol.* 48: 167, 1955.
56. Fisher, A. E. *Science* 124: 228, 1956.
57. Freeman, W. and J. W. Watts. *Psychosurgery* (2nd ed.). Springfield: Thomas, 1950.
58. Freud, S. *New Introductory Lectures on Psycho-analysis*. New York: Norton, 1933.
59. Fulton, J. F. *Frontal Lobotomy and Affective Behavior*. New York: Norton, 1951.
60. Gellhorn, E. *Autonomic Regulations*. New York: Interscience, 1943, frontispiece.
61. Gloor, P. *A. M. A. Arch. Neurol. & Psychiat.* 71: 773, 1954.
62. Gray, J. *Symp. Soc. Exper. Biol.* 4: 112, 1950.
63. Grier, M. A. *Proc. Soc. Exper. Biol. & Med.* 89: 59, 1955.
64. Guttman, N. *J. Comp. & Physiol. Psychol.* 47: 358, 1954.
65. Harlow, H. F. *Psychol. Rev.* 60: 23, 1953.
66. Harriman, A. E. *J. Nutrition* 57: 271, 1955.
67. Harris, L. J., J. Clay, F. J. Hargreaves and A. Ward. *Proc. Roy. Soc., London, ser. B* 113: 161, 1933.
68. Heath, R. G. *Psychosom. Med.* 17: 383, 1955.
69. Hebb, D. O. *Psychol. Rev.* 62: 243, 1955.
70. Hess, W. R. *Diencephalon: Autonomic and Extrapyramidal Functions*. New York: Grune, 1954.
71. Hetherington, A. W. and S. W. Ranson. *Am. J. Physiol.* 136: 609, 1942.
72. Hoskins, R. G. *Am. J. Physiol.* 72: 324, 1925.
73. Hunt, J. McV. and H. Schlosberg. *J. Comp. Psychol.* 28: 23, 1939.
74. Ingelfinger, F. J. *New England J. Med.* 231: 321, 1944.
75. Janowitz, H. D. and M. I. Grossman. *Am. J. Physiol.* 159: 143, 1949.
76. Jasper, H. H. In: *Brain Mechanisms and Consciousness*, edited by J. F. Delafresnaye. Springfield: Thomas, 1954, p. 374.
77. Kennard, M. A. *A. M. A. Arch. Neurol. & Psychiat.* 48: 227, 1942.
78. Kennard, M. A. and L. Ectors. *J. Neurophysiol.* 1: 45, 1938.
79. Kleitman, N. *Sleep and Wakefulness*. Chicago: Univ. Chicago Press, 1939.
80. Kleitman, N. and N. Camille. *Am. J. Physiol.* 100: 474, 1932.
81. Klüver, H. and F. C. Bucy. *A. M. A. Arch. Neurol. & Psychiat.* 42: 979, 1939.
82. Kohn, M. *J. Comp. & Physiol. Psychol.* 44: 412, 1951.
83. Kuo, Z. Y. *Psychol. Rev.* 31: 427, 1924.
84. Langworthy, O. R. and C. P. Richter. *Am. J. Physiol.* 126: 158, 1939.
85. Larsson, S. *Acta physiol. scandinav.* 32, Suppl. 115: 8, 1954.
86. Lashley, K. S. *Psychol. Rev.* 45: 445, 1938.
87. LeBlond, C. P. *J. genet. Psychol.* 57: 327, 1940.
88. Leeper, R. W. *J. genet. Psychol.* 46: 3, 1935.
89. Lehrman, D. S. *Quart. Rev. Biol.* 28: 337, 1953.
90. Lindsley, D. B. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951, p. 491.
91. Lindsley, D. B., J. Bowden and H. W. Magoun. *Electroencephalog. & Clin. Neurophysiol.* 1: 475, 1949.
92. Magoun, H. W. In: *Brain Mechanisms and Consciousness*, edited by J. F. Delafresnaye. Springfield: Thomas, 1954, p. 1.
93. Mayer, J. *Bull. New England Med. Center* 14: 43, 1952.
94. Mayer, J. *Ann. New York Acad. Sc.* 63: 15, 1955.
95. McCleary, R. A. *J. Comp. & Physiol. Psychol.* 46: 411, 1953.
96. McDougall, W. *An Introduction to Social Psychology*. London: Methuen, 1908.
97. Miller, N. E. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951, p. 435.
98. Miller, N. E. *J. Personality* 20: 82, 1951.
99. Miller, N. E. *Ann. New York Acad. Sc.* 63: 141, 1955.
100. Miller, N. E. *Ann. New York Acad. Sc.* 65: 318, 1956.
101. Miller, N. E. *Science* 126: 1271, 1957.
102. Miller, N. E., C. J. Bailey and J. A. F. Stevenson. *Science* 112: 256, 1950.
103. Miller, N. E. and M. L. Kessen. *J. Comp. & Physiol. Psychol.* 45: 555, 1952.
104. Miller, N. E., R. I. Sampliner and P. Woodrow. *J. Comp. & Physiol. Psychol.* 50: 1, 1957.
105. Montemurro, D. G. and J. A. F. Stevenson. *Canad. J. Biochem. & Physiol.* 35: 31, 1957.
106. Montgomery, A. V. and J. H. Holmes. *Am. J. Physiol.* 182: 227, 1955.
107. Morgan, C. T. *Physiological Psychology*. New York: McGraw-Hill, 1943, p. 294.

108. Morgan, C. T. and J. D. Morgan. *J. genet. Psychol.* 57: 153, 1940.
109. Morgan, C. T. and E. Stellar. *Physiological Psychology.* New York: McGraw-Hill, 1950, chap. 16, 17, 18, 19, 20.
110. Munn, N. L. *Handbook of Psychological Research on the Rat.* Boston: Houghton, 1950, p. 52, 85.
111. Murray, H. A. *Explorations in Personality.* New York: Oxford, 1938.
112. Nauta, W. J. H. *J. Neurophysiol.* 9: 285, 1946.
113. Olds, J. *J. Comp. & Physiol. Psychol.* 49: 281, 1956.
114. Olds, J. and P. Milner. *J. Comp. & Physiol. Psychol.* 47: 419, 1954.
115. Pfaffmann, C. *J. Neurophysiol.* 18: 429, 1955.
116. Pfaffmann, C. and J. K. Bare. *J. Comp. & Physiol. Psychol.* 43: 320, 1950.
117. Pilgrim, F. J. and R. A. Patton. *J. Comp. & Physiol. Psychol.* 40: 343, 1947.
118. Porter, R. W., E. B. Cavanaugh, B. V. Critchlow and C. H. Sawyer. *Am. J. Physiol.* 189: 145, 1957.
119. Pribram, K. H. and J. F. Fulton. *Brain* 77: 34, 1954.
120. Pribram, K. H. and L. Weiskrantz. *J. Comp. & Physiol. Psychol.* 50: 74, 1957.
121. Ranson, S. W. *A. M. A. Arch. Neurol. & Psychiat.* 41: 1, 1939.
122. Ranson, S. W. *A. Res. Nerv. & Ment. Dis., Proc.* 20: 342, 1940.
123 Ranson, S. W., H. Kabat and H. W. Magoun. *A. M. A. Arch. Neurol. & Psychiat.* 33: 467, 1935.
124. Reid, L. S. and F. W. Finger. *J. Comp. & Physiol. Psychol.* 48: 110, 1955.
125. Richter, C. P. *Quart. Rev. Biol.* 2: 307, 1927.
126. Richter, C. P. *Am. J. Physiol.* 115: 155, 1936.
127. Richter, C. P. *Am. J. M. Sc.* 198: 9, 1939.
128. Richter, C. P. *Endocrinology* 24: 367, 1939.
129. Richter, C. P. *Harvey Lectures* 38: 63, 1942–43.
130. Richter, C. P. *J. Comp. & Physiol. Psychol.* 40: 129, 1947.
131. Richter, C. P. and K. H. Campbell. *J. Nutrition* 20: 31, 1940.
132. Richter, C. P. and C. D. Hawkes. *J. Neurol. & Psychiat.* 2: 231, 1939.
133. Ruch, T. C. and H. A. Shenkin. *J. Neurophysiol.* 6: 349, 1943.
134. Rundquist, E. A. *J. Comp. Psychol.* 16: 415, 1933.
135. Schreiner, L. and A. Kling. *J. Neurophysiol.* 16: 643, 1953.
136. Schreiner, L. and A. Kling. *A. M. A. Arch. Neurol. & Psychiat.* 72: 180, 1954.
137. Schreiner, L., D. McK. Rioch, C. Pechtel and J. H. Masserman. *J. Neurophysiol.* 16: 234, 1953.
138. Scott, E. M. *Tr. Am. A. Cereal Chemists* 6: 126, 1948.
139. Scott, E. M. and E. L. Verney. *J. Nutrition* 34: 471, 1947.
140. Share, L., E. Martyniuk and M. I. Grossman. *Am. J. Physiol.* 169: 229, 1952.
141. Sidman, M., J. V. Brady, J. J. Boren and D. G. Conrad. *Science* 122: 830, 1955.
142. Siegel, P. S. *J. Psychol.* 21: 227, 1946.
143. Skinner, B. F. *The Behavior of Organisms.* New York: Appleton, 1938, p. 341.
144. Smith, K. U. *Psychol. Bull.* 39: 493, 1942.
145. Smith, O. A. *Anat. Rec.* 124: 363, 1956.
146. Solomon, R. L. and E. S. Brush. In: *Nebraska Symposium on Motivation,* edited by M. R. Jones. Lincoln: Univ. Nebraska Press, 1956, p. 212.
147. Sprague, J. M. and W. W. Chambers. *Am. J. Physiol.* 176: 52, 1954.
148. Stamm, J. S. *J. Comp. & Physiol. Psychol.* 47: 21, 1954.
149. Stamm, J. S. *J. Comp. & Physiol. Psychol.* 48: 347, 1955.
150. Steggerda, F. R. *Am. J. Physiol.* 132: 517, 1941.
151. Stellar, E. *Psychol. Rev.* 61: 5, 1954.
152. Stellar, E. and J. H. Hill. *J. Comp. & Physiol. Psychol.* 45: 96, 1952.
153. Stellar, E., R. Hyman and S. Samet. *J. Comp. & Physiol. Psychol.* 47: 220, 1954.
154. Stellar, E. and R. A. McCleary. *Am. Psychologist* 7: 256, 1952.
155. Stowe, F. R. and A. T. Miller. *Experientia* 13: 114, 1957.
156. Teitelbaum, P. *J. Comp. & Physiol. Psychol.* 48: 156, 1955.
157. Teitelbaum, P. and E. Stellar. *Science* 120: 894, 1954.
158. Tinbergen, N. *The Study of Instinct.* Oxford: Clarendon Press, 1951.
159. Tsang, Y. C. *J. Comp. Psychol.* 26: 1, 1938.
160. Verney, E. B. *Proc. Roy. Soc., Lond. Ser. B* 135: 24, 1947.
161. Wald, G. and B. Jackson. *Proc. Nat. Acad. Sc., Washington* 30: 255, 1944.
162. Wang, G. H. *Comp. Psychol. Monogr.* 2: No. 6, 1923.
163. Wangensteen, O. H. and A. J. Carlson. *Proc. Soc. Exper. Biol. & Med.* 28: 545, 1931.
164. Warden, C. J. *Animal Motivation Studies: The Albino Rat.* New York: Columbia, 1931.
165. Watson, J. B. *Behaviorism.* New York: Norton, 1925.
166. Weiner, I. H. and E. Stellar. *J. Comp. & Physiol. Psychol.* 44: 394, 1951.
167. Wheatley, M. D. *A. M. A. Arch. Neurol. & Psychiat.* 52: 296, 1944.
168. Wilder, C. E. *J. Comp. Psychol.* 24: 547, 1937.
169. Wilkins, L. and C. P. Richter. *J. A. M. A.* 114: 866, 1940.
170. Wolfe, J. B. *Comp. Psychol. Monogr.* 12: No. 60, 1936.
171. Woodworth, R. S. and H. Schlosberg. *Experimental Psychology.* New York: Holt, 1954, p. 664.
172. Young, P. T. *J. Comp. Psychol.* 37: 327, 1944.
173. Young, P. T. *Comp. Psychol. Monogr.* 19: No. 5, 1949.
174. Zeaman, D. *J. Exper. Psychol.* 39: 466, 1949.

CHAPTER LXIII

# Emotional behavior

JOSEPH V. BRADY | *Walter Reed Army Institute of Research, Washington, D.C., and University of Maryland, College Park, Maryland*

CHAPTER CONTENTS



THE SUBJECT MATTER which provides the title for the present chapter has long occupied the attention of biological scientists concerned with the general problems of behavior and the related events of an organism's physiology. Our understanding of the relationships between organismic-environmental interactions referred to as 'emotional' and the 'structure-function' properties of the nervous system, in particular, has evolved slowly and somewhat haltingly, however, amidst a host of psychological and physiological complexities. Introspective emphasis upon the phenomenological or 'feeling' aspect of the 'emotion' problem has occupied a prominent place in the development of many highly speculative theories. Such basic scientific descriptions of this subject matter as we do have at present and are likely to attain in the future, however, would seem to depend upon the experimental analysis of expressive or behavioral phenomena, objectively and operationally defined. Similarly, although the measurement of more peripheral bodily changes related to such affective processes has been extensively described, the direct analysis of neurological mechanisms associated with emotional behavior has only recently begun to take firm anatomical and physiological form.

In approaching the general topic of emotional behavior within the framework of this *Handbook*, emphasis will most appropriately focus upon related neurophysiological events. Some brief consideration will first be given to the psychological or behavioral aspects of the problem, however, as they relate specifically to the defining properties of the organism's interaction with the environment and the participating events of the nervous system. Against this background, we can then proceed to consider some of the methodological approaches which have characterized the half century or more of biological research in this problem and the contributions made toward the elucidation of central organization in emotional behavior. With this perspective, more recent developments in the anatomical, physiological and behavioral analysis of affective processes can be considered with a view to elaborating observed relationships and assessing the present status and future outlook for this problem. Certainly, we shall not hesitate to pause along this charted course to spend some time with an interesting finding or a new development, but the general direction and scope of our coverage will adhere reasonably well to this broad outline.

## SOME PSYCHOLOGICAL CONSIDERATIONS

In probably no other domain of psychological science has so little empirical data provided the occasion for so much theoretical speculation as in the general area of the 'emotions.' For the most part, the

voluminous literature on this topic reveals a phenomenological emphasis upon the 'affective' or 'feeling' aspects of the problem, and the wide range of digestive, respiratory, secretory and cardiovascular changes presumably related to emotional experience. Certainly, the classical James-Lange formulation (111, 201, 234) and even Cannon's 'neural organization' theory of emotion (69, 72) can be seen to share this experiential emphasis. And indeed, the ever-popular Freudian view of emotional processes as 'mental states' or 'psychic phenomena' (128) continues to pervade even the most sophisticated treatments of the topic. The history of psychological speculation, however, has not been devoid of attempts to deal with the emotions behavioristically, if, at times, somewhat introspectively. The roots of such approaches are to be found even as far back as Darwin's early attention to the facial musculature in his consideration of the evolutionary aspects of emotional expression (93) and Wundt's emphasis upon the emotions as 'conscious contents' (402). Furthermore, Watson's classical treatment of the emotions as conditioned phenomena emphasized interactions between the organism and its environment as the focus for his behavioristic views (383, 384). More recently, this descriptive behavioristic tradition has found expression in Skinner's analysis of emotion in terms of the probability or predisposition to change of a more or less broad range of behavioral response patterns (347), and in the related view of Keller & Schoenfeld that emotional behavior represents widespread changes in 'reflex strength' as a function of specific environmental contingencies (210). Many other more or less extreme theoretical views have characterized psychological speculation in this area, and the serious student of emotional behavior will not want to overlook these efforts (3, 20, 26, 43, 51, 106–109, 139, 164, 165, 172–174, 196, 205, 235, 237, 245, 248, 265, 273, 274, 276, 277, 280, 281, 292, 297, 302, 324, 325, 329, 352, 354, 368, 403).

Experimentally, attempts to define emotional behavior for laboratory investigative purposes have usually focused both upon antecedent stimulus events which appear to produce or provide the occasion for a given response pattern, and upon the characteristics of the response pattern per se. Typically, for example, both conditioned and unconditioned reactions associated with aversive stimuli have been regarded as 'emotional,' and a broad range of internal (e.g. epinephrine administration) and external (e.g. electric shock) environmental changes have become traditionally identified as the antecedents which define such behavioral events (51, 232). More frequently, however, the properties of a given response pattern per se appear to serve as the basis for classifying behavior as 'emotional.' Certain characteristics of an organism's muscular activity (e.g. vocalization, trembling) have been conventionally identified with affective phenomena, and extensive physiological processes (e.g. autonomic changes) have received wide acceptance as 'indicators' of 'emotional' participation in a behavioral situation. Despite extensive research effort in this direction (70, 110), however, it has not been possible to distinguish reliably between emotional activities either on the basis of specific antecedent stimulus events or observable muscular and autonomic response patterns. Even the identification of emotional behavior in general by these criteria has presented problems, since such stimulus and response events are frequently observed to occur under circumstances not conventionally associated with emotion, such as temperature changes or heavy exercise.

Faced with such difficulties, many psychological studies have focused upon the consequences of emotional situations for a broad spectrum of behavioral processes in an attempt to define emotion. Commonly, the disruptive or suppressing effects of emotional disturbance upon ongoing activity have received both clinical and experimental emphasis (6, 43, 114, 116, 129, 206, 236, 240, 243, 265, 273, 330, 403). The defining properties of emotional behavior segments, however, may as often involve an increased frequency or probability of adaptive response patterns, particularly when the contingencies of the situation require avoidance of aversive stimuli (281, 343, 352) or emergence of appetitive consequences (46, 115, 176, 378).

In the rather obvious absence of any completely satisfactory theoretical or experimental formulation of emotional behavior, the task of defining and delimiting the psychological subject matter for such a neurophysiological survey can be seen to present many difficulties. Conventional criteria for identifying emotional activities appear far from adequate, and the classification of emotions or differentiation of subtle 'strength' phenomena (from the 'milder effects' to the 'violent emotions') continues to elude definitive analysis. Certainly, the choice of material for the present treatment will, of necessity, appear arbitrary in many instances, and there will be legitimate questions concerning the appropriateness of much that has been included as well as much that has been omitted. Since our present level of psy-

chological sophistication would hardly seem to justify a more restrictive or provincial approach the dictates of conventional or traditional usage will determine, in large part, the character of our behavioral coverage. There can be little doubt that the results of future research efforts are likely to require extensive modification and reorientation of past and present thinking in this area. But the somewhat descriptive behavioristic framework within which much of the laboratory work on emotional behavior has proceeded should permit some realistic assessment of the past history, present status and future perspectives of a most complex psychophysiological problem.

## SOME HISTORICAL AND METHODOLOGICAL CONSIDERATIONS

For the most part, the measurement and analysis of bodily changes associated with emotional behavior have focused upon peripheral response mechanisms related principally to integration by the autonomic nervous system, the cerebrospinal system and the endocrine system. Dunbar's recent revision of her volume on *Emotions and Bodily Changes* (110) provides an exhaustive 4,717-item classified bibliography in this area. Several other authors have also described techniques for recording such peripheral changes and presented detailed experimental analyses of the characteristic physiological processes associated with more or less broadly defined affective phenomena (5, 70, 89, 95, 97, 146, 191, 228–230, 245, 248, 262, 266, 324, 392, 403, 404). Typically, studies in this general area have emphasized the relationship of the emotions to such peripheral phenomena as the electrical response of the skin (88, 163, 358, 390, 391), arterial pressure and blood volume (88, 239, 317, 337), electrocardiogram and heart rate (298, 317, 389, 396), respiration (66, 123) skin temperature (285, 286), pupillary changes (21, 253), salivary secretion (399, 400), pilomotor effects (250), dermographia (392), skin sweating (344, 393), changes in the chemical composition of blood, saliva and urine (104, 105, 140, 146, 149, 188, 261, 305, 399), gastrointestinal activity (27, 70, 261, 263, 264, 367), metabolic rate (248), muscle tension (65, 84, 94, 318), tremor (24, 254), and even eye blink and eye movements (249). In addition, of course, autonomic, endocrine and neurohumoral relationships have been extensively and somewhat more directly analyzed in the quest for a better understanding of emotional processes (69, 71–76, 146–148, 353). Certainly a comprehensive view of the affective process must not fail to take account of the intimate relationship between such peripheral physiological response expressions of emotion and the more central neural participants which provide the focus for the present neurophysiological analysis.

Methodologically, clinical and experimental observations related to central neural organization in emotional behavior have emerged from four major sources: *a*) laboratory ablation studies involving central nervous system structures, *b*) direct electrical or chemical stimulation of central nervous system structures, *c*) electrical recording from central nervous system tissue and *d*) clinical, including neurosurgical, observations. For many centuries, of course, more or less informal accounts of clinical changes in emotional behavior associated with pathological involvement of central nervous system function (e.g. epilepsy) have emerged from both medical and literary sources. It was not until the latter half of the nineteenth century, however, that the clinical acumen of Hughlings Jackson and the consequent dedication of men like Ferrier and Sherrington began to provide the foundations for systematic analysis of neurological mechanisms in emotional behavior and for subsequent emphasis upon development of the more experimental approaches which will receive primary emphasis in our present treatment. Since that time, a somewhat voluminous clinical literature on the psychological consequences of brain damage and related neurological disorders (83, 96, 126, 131, 168, 214, 216, 255, 278, 362) may be seen to have contributed both directly and indirectly to our understanding of central nervous system participation in emotional behavior. Necessarily, coverage of this clinical material will be highly selective within the relatively limited experimental scope of the present treatment, although related sections of this volume on autonomic activities and transactional mechanisms should provide a somewhat broader factual analysis of data pertinent to this general source.

Historically, ablation techniques can be seen to have provided the earliest laboratory approaches to the experimental analysis of neural mechanisms in emotional behavior. In the course of their more broadly conceived neurophysiological inquiries into cortical function, for example, Brown & Schäfer (67), reporting in the *Philosophical Transactions* as early as 1888, described 'emotional' changes in rhesus monkeys following temporal lobe lesions involving relatively

selective subcortical structures. The early observations of Goltz (156) toward the close of the last century on 'emotional' responses to mere handling in the decerebrate dog can be seen to provide the experimental beginnings for a laboratory analysis of neurological mechanisms in affective expression. With the turn of the century, ablation studies primarily concerned with only indirectly related neurophysiological problems continued to point up the ill-defined role of central neural processes in the organization of emotional behavior. In 1904, an investigation by Woodworth & Sherrington (401) of the spinal pathways related to pain revealed what they described as 'pseudoaffective' behavioral changes in the decerebrate cat. Within the first two decades of the century, the further observations of Dusser de Barenne (112) following acute decortication in the cat had begun to focus more directly upon emotional behavior changes associated with experimental manipulation of the nervous system.

Starting in the early 1920's, a rapid succession of experimental observations by Bazett & Penfield (19), Rothmann (323) and the now classic investigations of the decorticate preparation's 'sham rage' response by Cannon & Britton (73) further elaborated the specific character of central nervous system involvement in emotional expression. These early studies can be seen to have set the stage effectively for a host of experimental and theoretical efforts in this general direction which were to follow over the next three decades or more. Until well into the 1930's, however, ablation techniques combined with gross observation of expressive phenomena in the experimental animal provided virtually the only laboratory methods available to the investigator of central participation in emotional behavior. Indeed, Berger's pioneering work on the electrical activity of the nervous system (22) and even that of Hess on direct electrical stimulation methods (179) may be seen to have their origins at a somewhat earlier date; but the direct application of these important methodological developments to the analysis of central organization in emotional behavior was, understandably, to follow only a delay of several years. The striking changes in electrical activity of the brain, which were observed even by Berger to accompany 'attention' or 'anticipatory responsiveness' to sensory stimulation, early suggested the role electrical recording methods were to play in the elaboration of neural events associated with affective states. It was not until the later work of Lindsley (247), Darrow (90) and others (160, 186, 189, 364, 380, 397), however, that the more direct application of these methods to the problem of emotion was to make its firmest contribution. The studies of emotional behavior changes following direct stimulation of selective brain structures by Ranson & Magoun (315), Masserman (271, 273) and others (45, 99, 100, 168, 338), which were to follow Hess' fruitful lead (180, 182), did not appear in definitive form until after the late 1930's and the early 1940's.

Clearly, however, the 'modern era' in laboratory brain-behavior research related to the problem of emotions and the central nervous system can be seen to date from the now classical presentation before the 1937 meetings of the American Physiological Society by Klüver & Bucy (217) reporting dramatic emotional behavioral alterations produced by rather extensive temporal neocortical and paleocortical lesions in the rhesus monkey. A few months later, Papez's speculative paper on "A Proposed Mechanism of Emotion" (302) appeared with its emphasis upon primarily paleocortical, juxtallocortical and related subcortical structures; and in the following two decades, numerous anatomical, neurophysiological and behavioral studies have testified to the truly remarkable perspicacity of these early efforts. This enduring interest in the neural substrata of emotional behavior has had the not inconsiderable advantage of important technical and investigative advances in neuroanatomy (150, 295, 296, 369) and neurophysiology (98, 138, 199, 259, 291) over the past decade or more, not to mention the many more recent developments in behavioral control techniques (121, 122, 346). Such combined methodological skills have been profitably applied to the experimental analysis of affective processes (15, 43, 45, 46, 51, 53, 54, 170, 274, 342). Indeed, some reflection of the degree and direction of this progress in this interdisciplinary approach is to be found in the recent appearance of several excellent comprehensive reviews directly related to this subject (132, 216, 255, 311).

## NEUROPHYSIOLOGICAL DEVELOPMENTS AND BRAIN-BEHAVIOR RELATIONSHIPS

### *Midbrain Reticular Influences*

Probably the first systematic experimental efforts to suggest differential participation of nervous system components in the elaboration of emotional behavior

can be safely attributed to Goltz (156) and to Woodworth & Sherrington (401) in their analysis of the 'pseudoaffective' behavioral reactions which are observed to follow transection of the brain stem at the intercollicular level in laboratory carnivores. Nociceptive stimulation of the skin in such preparations can be seen to elicit mimetic expressions of apparent 'anger' and 'rage' in the form of growling, barking, opening of the mouth, retraction of lips and tongue, snapping of jaws, snarling, lowering of the head as if to attack, and increase in arterial pressure. All such responses are extremely brief and do not outlast stimulation, however, and the normal emotional repertoire of such preparations appears severely circumscribed, especially with respect to the more positive types of affective expression usually present in unoperated members of these species (apparent 'joy' or 'satisfaction,' and sexual behavior). Indeed, many later observations have confirmed the general appearance of a poorly organized 'rage' response of but brief duration in the decerebrate preparation, along with a number of associated sympathetic reactions, although in not all cases does there seem to be a complete absence of pleasurable reaction (19, 208, 323, 328). The main point of interest to be derived from these observations, however, is that at least some primitive 'pseudoaffective' behavioral expressions of emotion can be readily elicited at this midbrain level even in the absence of all other forebrain structures. Section of the brain stem below this level, however, has been reported by Bard (11) to abolish such behavior and strongly suggests involvement of the midbrain reticular formation in the mediation of at least these rather fundamental aspects of emotional expression. Certainly, a host of important subsequent experimental observations (16, 96, 127, 211, 251) have continued to draw attention to reticular influences in many basic features of the emotional behavior pattern and in the maintenance of 'aroused affective states.' Lindsley (248) has recently proposed an 'activation theory of emotion' which assigns critical executive functions to the reticular formation of the brain stem.

*Diencephalic Participation*

The more classic theoretical conceptions relating emotional behavior and the nervous system can be seen to have developed around experimental emphasis upon cortical-diencephalic interrelationships. The early experiments of Dusser de Barenne (112) and Cannon & Britton (73), using decorticate preparations and the now famous 'sham-rage' phenomena characteristic of such animals, did indeed provide an early focus for this continuing emphasis upon forebrain mechanisms in emotional expression. By comparision with the more drastic Sherringtonian decerebrates, the decorticate preparations can be observed to respond even more readily and in a somewhat more intense, better organized fashion to ordinary handling and care, although the behavior remains poorly directed and short-lived. As a matter of fact, subsequent experimental analysis by Bard and Rioch (10–13, 17, 319) clearly demonstrated that such sham-rage behavior (described in some detail by these authors as involving lowering of the head and body in crouch, raising the back, drawing back the ears, loud angry growling, hissing, biting, striking with claws unsheathed, erection of hair, pupillodilatation, retraction of nictitating membrane, and widening of palpebral fissures) could still be elicited after removal of all cerebral tissue rostral, dorsal and lateral to the hypothalamus (including virtually all of the paleocortex, juxtallocortex and major portions of the related subcortical structures). This vigorously patterned but poorly directed activity involving both somatic and visceral components failed to develop, however, following truncation of the brain stem at any level below the caudal hypothalamus, a consideration suggesting both the central executive and facilitatory functions of these diencephalic regions in the elaboration of emotional behavior, as well as the possible inhibitory role of more rostral neocortical and paleocortical forebrain structures. It is interesting to note in this connection that even a somewhat broader range of affective expression, including 'fear' and 'sexual excitement,' in addition to the sham-rage response, was also described by Bard and Rioch as being elicitable from such preparations with extensive forebrain damage. More recent observations by Bromiley (61), in the course of discrimination learning experiments with the decorticate dog, seem to indicate that the capacity for affective expression in such preparations can be maintained over relatively long periods of time even in the absence of extensive forebrain influences. Barking, growling, snarling and snapping as characteristic components of the sham-rage response to mere cage manipulation or gentle handling persisted over an extended period of almost 3 years in the Bromiley decorticate preparation. Clearly this important combination of experimental inquiries points up the striking facilitatory role exerted by the addition of limited (although obviously critical) hy-

pothalamic influences to the more primitive reticular activating mechanisms.

The continuing emphasis upon hypothalamic mechanisms in the development of neurophysiological approaches to the experimental analysis of emotional behavior has shown no diminution over the several decades that have intervened since these early explorations. Subsequent efforts have provided convincing evidence of the central but somewhat complicated role played by hypothalamic portions of the forebrain in the elaboration of affective phenomena. The monumental studies of Hess and his collaborators (152, 155, 181–183) have demonstrated the broad range of emotional response patterns which can be selectively elicited from discretely localized electrical stimulation of carefully mapped diencephalic regions. The behavior changes observed following such direct stimulation of the hypothalamus have been compared with alterations seen in emotional responses of normal animals conventionally associated with 'fear,' 'anger' and 'pleasure,' as well as with such phenomena as 'exploratory tendencies, feeding tendencies, cleaning tendencies and continuous restlessness.' In general, the results of these studies have indicated that more anterior and lateral portions of the diencephalon, including the basal septal nuclei, the preoptic area, the lateral hypothalamus and part of the basal medial thalamus, may be associated with hostile and aggressive 'rage' responses, or 'affective defense reactions' as Hess prefers to call them. As stimulation is carried more posteriorly, changes in oral behavior, increased restlessness and escape responses appear, although no clear-cut topographical arrangement of hypothalamic nuclei with specific functional significance for affective processes has yet been discerned. Indeed, Ranson (314, 315), Ingram (197, 198), Masserman (271–273) and others (187, 207) have also demonstrated the emotionally exciting effects ('fear' and 'rage' responses with multiple sympathetic manifestations) of direct hypothalamic stimulation in cats and monkeys, and at least some partial confirmation of hypothalamic involvement in emotional activities has been obtained by White (395) with electrical stimulation methods in conscious human patients under local anesthesia. In addition, Grinker (159) also recorded selective electrical activity from deep-lying hypothalamic electrodes in man in response to 'emotional probing.' And, of course, the recent emergence of experimental emphasis upon results obtained with intracranial self-stimulation techniques, following the interesting demonstration by Olds & Milner (301) of the rewarding effects associated with direct electrical stimulation of selective forebrain structures, has suggested the intimate participation of hypothalamic influences, among others, in the presumably affective components of this phenomenon in a wide variety of species (46, 299, 300).

That the hypothalamic role in the mediation of affective behavior is not to be regarded as unitary or uncomplicated, however, has been even more clearly emphasized by the results of numerous ablation studies involving relatively discrete destruction of selected diencephalic nuclei and the analysis of behavioral changes. Bilateral lesions in the caudal part of the hypothalamus of cats and dorsolateral to the mammillary bodies in the monkey were early reported by Ingram *et al.* (198) and by Ranson (314) to produce complete loss of emotional responsiveness (masklike faces, stolidity), and sometimes somnolence and sleep. Similar results were also obtained by Masserman (270), although reports of his own experiments in this area stress metabolic and homeostatic changes in accounting for the apparently transient emotional effects of such lesions. In contrast, Kessler (213) and Wheatley (394) have shown that destruction of the more medial aspects of this diencephalic region can result in dramatic rage reactions. In the more extensive study by Wheatley, relatively small lesions in the ventromedial hypothalamic nuclei were observed to produce 'extremely, chronically and incurably savage' behavior in cats. Interestingly, however, the rage reactions in these animals (which appeared 'not unmixed with fear') were not blind or senseless, but well-directed and coordinated, complete with all the normal autonomic phenomena and well-calculated defensive and offensive activities. Nor were these ventromedial rage reactions altered appreciably by superimposition of partial or total frontal lobectomy, removal of the temporal neocortex, or destruction of the mammillothalamic tracts, the fornices at the septal level, the dorsomedial thalamic nuclei or the mammillary bodies (197). Differential changes in cerebral cortical potential patterns have also been recorded with implanted electrodes from such ventromedial hypothalamic preparations (199).

Practically all the behavioral alterations observed to follow ablation and stimulation of the hypothalamus in experimental animals have also been reported in man after trauma, operative manipulation, tumor, vascular lesions and infections of the hypothalamus.

Although precise anatomical localization of specific diencephalic regions tends to be far from satisfactory under such conditions, various manifestations of affective changes including 'terror,' 'rage,' 'anxiety' and even some of the more 'pleasant moods' ('witty,' 'jocular,' 'obscene') have been reported following hypothalamic involvement in the human (1, 80, 82, 85, 87, 124, 134, 385, 395). And indeed, both experimental and clinical observations over the past three decades have made it abundantly clear that many other important biological motivations intimately related to emotional expression, including hunger, thirst, sleep, sex and activity, bear a critical dependence upon the functional integrity of relatively specific hypothalamic components (2, 14, 58, 62–64, 85, 134, 184, 294, 314, 316, 375, 385). This diencephalic emphasis has, as a matter of fact, found most recent expression in Stellar's (360) presentation of a 'physiological theory of motivated behavior' which places a heavy explanatory burden upon hypothalamic excitation in accounting for a wide range of motivational-emotional behavior patterns.

The weight of available evidence, then, would certainly seem to indicate that at least some primitively organized, relatively undifferentiated patterns of emotional behavior may be elaborated within limited reticular and hypothalamic levels of neural organization. The emergence of homeostatic and adaptive autonomic functions, as well as important somatomotor activities basic to such affective processes, would seem to depend critically upon the unique and direct integration of such brain-stem components with peripheral effector mechanisms. But the functional limitations of such gross reaction patterns contrast sharply with the more delicately balanced and restrained discriminative emotional behavior of which the normal organism is seen to be capable. Quite obviously, important influences from more advanced forebrain levels of integration contribute significantly to the elaboration and refinement of complexly organized and finely differentiated emotional response repertoires. Indeed, the early writings of Head (167) and the subsequent theoretical formulations of Cannon (69, 72) suggested an important role for the more rostral thalamic nuclei in the elaboration of these affective processes, and several clinical and experimental inquiries over the past two decades have clearly justified this speculative focus.

Spiegel and his collaborators (356, 357), for example, have reported changes in emotional behavior in both experimental animals and human patients following various thalamic lesions, involving principally the dorsomedial nuclei. Such ablations appear to reduce 'anxiety,' 'tension,' 'agitation' and 'aggressive or assaultive behavior' in psychiatric patients, and at least a transitory reduction in emotional reactivity was presumably observed in similarly operated animals. More extended observations, however, by Schreiner *et al.* (335) on such animal preparations (cats) with lesions rather carefully restricted to the thalamic dorsomedial nuclei, demonstrate emotional changes in the direction of 'increased irritability and rage,' even though there has been some confirmation of an 'amelioration of neurotic patterns' in some of the same animals (275, 303). Of course, many of these same experimental studies have implicated more extensive regions of the thalamus, including the anterior and intralaminar nuclei (275, 335), and even some of the more posterior nuclear groups (356) in the elaboration of emotional changes, although reports of negative findings have likewise made important contributions (79). Delgado (99), however, has recently reported elicitation of 'conditioned anxiety, defensive and offensive movements, vocalizations, and autonomic manifestations' in both cats and monkeys electrically stimulated in the posteroventral nucleus of the thalamus. Olds (300) also finds at least some mildly rewarding effects as a result of intracranial self-stimulation in the rat from such diverse thalamic placements as the habenula, and the lateral, ventral and ventromedial nuclei.

The anterior nuclei, however, appear to have invited at least some special attention in the experimental quest for thalamic participants in emotional behavior. For the most part, lesions in this region of the thalamus in the cat are reported to produce marked reductions in emotional responsiveness (8, 275, 335), while the effects of direct electrical stimulation in the anterior thalamus appear to be at least 'alerting' in the cat (8) and highly rewarding in the rat (300). The range of these emotional changes following thalamic involvement suggests the possibility of a limited modulation of affective processes at this diencephalic level, even though the intimate relationship of these thalamic nuclei with more advanced paleocortical, juxtallocortical and neocortical systems must provide for the more refined and integrative behavioral expression. Certainly, both the structural and functional interaction between the mediodorsal thalamus and the frontal neocortex on the one hand,

and between the anterior thalamus and the cingulate gyrus on the other, would seem to suggest the framework within which this forebrain integrative process in emotional behavior may be best understood. It is through the latter of these two systems that the anterior nucleus of the thalamus can interact with the 'limbic system' circuits receiving so much contemporary emphasis in the analysis of emotional behavior (45, 132, 133, 155, 216, 255–260, 311).

*The Limbic System*

The early reference by Broca (59) to 'le grand lobe limbique' as a common denominator in all mammalian brains, and Papez' (302) subsequent theoretical speculations on a possible anatomical 'mechanism of emotion,' long ago suggested the potential mediating role of the 'limbic system' in affective processes. In general terms, Papez' proposal focused upon the more medial aspects of the cerebral hemispheres and emphasized the transmittal of the 'central emotive process of cortical origin built up in the hippocampal formation' (hippocampus, hippocampal gyrus, dentate gyrus and amygdala) via the fornix to the mamillary bodies. Efferents from this hypothalamic center were then presumed to course both downward to the brain stem and lower effector mechanisms, and upward through the mammillothalamic tract to the anterior thalamic nuclei, and onward to the cingulate gyrus, Papez' candidate for the 'cortical receptive and association area' for affective behavior. It was Papez' view "that the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus, and their connections constitute a harmonious mechanism which may elaborate the functions of central emotion, as well as participate in emotional expression." Certainly, Papez' delimitation of these structures as bearing an important relationship to emotional behavior, and his concomitant prediction of symptomatic changes associated with involvement of this 'anatomic circuit,' can in the light of subsequent clinical and experimental developments be seen to represent a considerable tour de force. The morphological and functional characteristics of this 'limbic system' have been more precisely defined and elaborated over the two decades since this original proposal, and several systematic attempts have been made to order the obviously complex interrelationships between these structures and other nervous system components according to both anatomicophysiological and behavioral principles (45, 155, 161, 175, 215, 216, 255, 256, 258, 259, 299, 311).

Despite these recent efforts, however, there is no general agreement as to the definition of morphological formations to be subsumed under the several presumably synonymous terms ('rhinencephalon,' 'visceral brain,' 'paleocortex,' etc.) used to refer to these groups or systems of functionally related forebrain structures associated with emotional behavior. Figure 1 illustrates diagrammatically some of the more prominent anatomical interrelationships which characterize the medial aspects of the hemisphere (45, 295, 320) and which provide at least some basis for considering the functional properties of these 'limbic system' structures within three general groups or classes as follows.

First, the paleocortical or allocortical portions of the system can be distinguished as those surface structures which meet the criteria for 'cortex' suggested by Rose & Woolsey (320) (a composition of at least three layers with the superficial layer constituting a fiber layer) and which also have clear phylogenetic primacy. These structures include the hippocampus (Ammon's horn and the dentate gyrus), the pyriform lobe (prepyriform cortex, periamygdaloid cortex and entorhinal area) and the olfactory bulb and tubercle.

Secondly, the juxtallocortical portions of the system define that group of cortical regions which are intermediate in position between the phylogenetically old paleocortex and the phylogenetically young neocortex, most of which have demonstrable anatomical connections with paleocortical structures. Such juxtallocortical regions include the cingulate gyrus or 'limbic cortex' (60, 349), the presubiculum and the 'frontotemporal' cortex, as recently defined by Pribram & Kruger (311).

Finally, a third group of subcortical structures (not meeting the criteria for 'cortex') which have been shown to be intimately related both anatomically and functionally to the paleocortex and juxtallocortex must be considered as part of the 'limbic system,' most broadly defined. These would include the amygdaloid complex, the septal region (septal nuclei and the nucleus of the diagonal band), certain thalamic and hypothalamic nuclei, and possibly even the caudate nucleus and midbrain reticular formation.

Unfortunately, most of these structures were formerly believed to be involved in mechanisms of olfaction and are even presently referred to in most standard didactic sources as the 'olfactory brain'

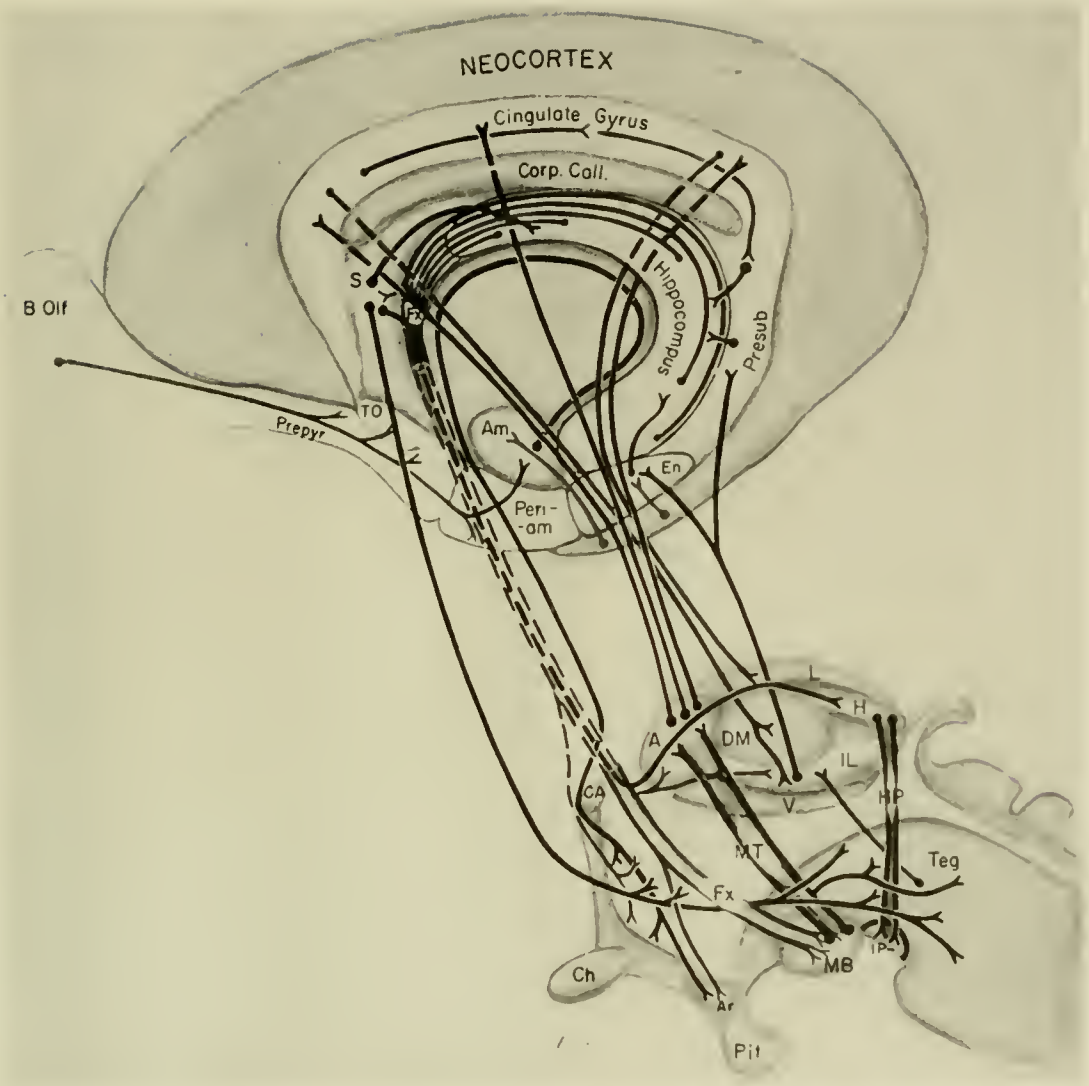



FIG. 1. Semidiagrammatic representation of the principal anatomical relationships between the 'paleocortex,' the 'juxtallocortex' and the several 'subcortical structures' considered in recent treatments of the 'limbic system.' The brain-stem portions of the system have been schematically displaced from the hilus of the hemisphere and represented in the *lower half* of the figure in order to facilitate visualization of the numerous anatomical interconnections involving these structures. *A*, anterior nucleus of the thalamus; *Am*, amygdaloid complex; *Ar*, arcuate nucleus; *B. Olf.*, olfactory bulb; *CA*, anterior commissure; *Ch*, optic chiasm; *Corp. Call.*, corpus callosum; *DM*, dorsomedial nucleus of the thalamus; *En*, entorhinal area; *Fx*, fornix; *H*, habenular complex; *HP*, habenulointerpeduncular tract; *IL*, intralaminar thalamic nuclei; *IP*, interpeduncular nucleus; *L*, lateral thalamic nucleus; *MB*, mammillary bodies; *MT*, mammillothalamic tract; *Periam*, periamygdaloid cortex; *Pit*, pituitary; *Prepyr*, prepyriform cortex; *Presub*, presubiculum; *S*, septal region, *Teg*, midbrain tegmentum; *TO*, olfactory tubercle; *V*, ventral nucleus of the thalamus. [From Brady (45).]

(311). This view, which tends to be perpetuated by the broad usage of the term rhinencephalon (216), would presently appear to be untenable in the light of recent studies (81, 125) which have clearly demonstrated a more restricted distribution of primary olfactory afferents (i.e. of fibers originating from the olfactory bulb). On the basis of this evidence, the term rhinencephalon should not be used synony-

mously with limbic system in referring to forebrain participants in affective processes but should be restricted to those structures subserving olfactory functions, including the olfactory bulb and tubercle, prepyriform and periamygdaloid cortex, some of the nuclei of the amygdaloid complex, and the bed nucleus of the stria terminalis.

Almost simultaneously with the 1937 publication of Papez' theoretical effort, Klüver & Bucy reported their most striking demonstration of the important participant role which rather extensive 'limbic system' components could be expected to play in the balancing, integration and elaboration of critically profound motivational-emotional behavior patterns. These now classic experiments (217–219), defining dramatic behavioral changes in monkeys following temporal neocortical and paleocortical lesions involving the frontotemporal cortex, pyriform lobe, amygdaloid complex, presubiculum and hippocampus, are now too well known to require detailed review. The broad range of behavioral alterations observed in these preparations, however, can be seen to bear directly upon the central problem of nervous system participation in affective processes. The formerly wild and intractable rhesus macaques used in these experiments became tame and docile, showing signs of neither fear nor anger, following this rather extensive involvement of the limbic system. They would not fight or retaliate when abused by other monkeys and also displayed what the authors refer to as 'psychic blindness,' oral tendencies and hypermetamorphosis, a kind of compulsive behavior. They behaved as if they could no longer discriminate between objects that were either potentially dangerous or useful to them. Such an animal would, as if by compulsion, smell and mouth everything (dirt, feces, nails, food) that captured its attention. Unless the object were edible, it was immediately dropped. If presented with a nail 100 times in succession, the animal would smell and mouth it each time as though he had not examined it before. Finally, these animals showed striking changes in sexual behavior; they appeared hypersexed, masturbated excessively, sought partnership with male or female indiscriminately, and manifested bizarre oral sexual behavior. Of particular interest, too, was the fact that when unilateral excision of only one lobe was accomplished, or when bilateral lesions were restricted to the temporal neocortex and spared the limbic system structures, the animals failed to show any of these dramatic changes in behavior.

Against the background of these early experimental and theoretical efforts, a host of important subsequent neurophysiological and neuropsychological developments have continued to broaden the base for a more thorough understanding of extensive limbic system components involved in the mediation of emotional behavior. Within a few short months of these first reports, Spiegel and his co-workers (355) clearly demonstrated the dramatic participation of the more rostral portions of the limbic system (including the olfactory tubercle and septal region) in rather complicated motivational-emotional behavior patterns. 'Sham-rage' reactions were observed by these authors following bilateral lesions confined to the olfactory tubercle and septal region in both cats and dogs, while similar effects resulted from involvement of the anterior amygdaloid nuclei, parts of the hippocampus, and the fornix. Indeed, a somewhat earlier report by Fulton & Ingram (135) had described similar 'rage' reactions in cats following bilateral prechiasmal lesions at the base of the brain, and more recent reports by Brady & Nauta (53, 54) confirm these findings in the rat. In addition, a recent publication by Heath *et al.* (168) further reflects the participant role of these more rostral limbic system components in the elaboration of emotional behavior, and the most dramatic demonstrations of rewarding effects consequent upon direct electrical stimulation of these same anteriorly placed limbic structures (including the orbital surface of the frontal lobes, the head of the caudate nucleus and the anterior hypothalamus) (46, 300, 301, 342) would seem to establish firmly their involvement in affective processes.

The most extensive and systematic research program initiated by Bard & Mountcastle (15, 16) within the decade following the report by Klüver & Bucy represents an important landmark in the further experimental analysis of limbic system relationships and emotional behavior. Concerned primarily with the role of forebrain mechanisms in the expression of 'rage' and 'angry behavior,' their initial experiments with cats showed that removal of all neocortex, while sparing the paleocortical, juxtallocortical and related subcortical components of the limbic system, produced a markedly placid and emotionally unresponsive animal. In the authors' view, these results indicated that portions of the limbic system, either singly or in concert, could exert a restraining influence upon lower brain mechanisms of demonstrated prepotence in the mediation of gross affective expression. Moreover, subsequent experiments in this same series

strongly suggested that the amygdaloid complex or cingulate gyrus, or both, might be specifically involved in the mediation of this restraining influence in the absence of the neocortex since rather striking increases in emotional reactivity followed removal of these subcortical and juxtallocortical structures in the previously neodecorticate preparation. More recently, Rothfield & Harman (322) have confirmed the placidity and emotional unresponsiveness resulting from neocortical ablation sparing the limbic system in cats, and have further demonstrated that the fornix (distributing important hippocampal fibers to the septal region, diencephalon and rostral midbrain) may figure prominently in the mediation of such restraining influences. Interruption of the fornix in their neodecorticate preparations resulted in a significant lowering of the rage threshold.

Bard & Mountcastle (15) further analyzed the effects of relatively discrete paleocortical, juxtallocortical and related subcortical lesions in otherwise intact cats in an attempt to delimit more precisely the character of limbic system participation in such behavioral phenomena. Although bilateral removal of the hippocampus and presubiculum produced little demonstrable alteration in affective expression (with the possible exception of slight increases in pleasureable reactions), bilateral removal of the pyriform lobe and amygdaloid complex (sparing other limbic structures) resulted in dramatic, if somewhat delayed, behavioral changes. In this particular case, the cats were observed to develop a markedly lowered rage threshold within 6 to 8 weeks following surgery, although subsequent reports by Gastaut and his collaborators (141, 288) and by Schreiner & Kling (332, 334) describe changes more in the direction of the Klüver-Bucy effect (218, 219) consequent upon similar (but obviously not precisely the same) destruction of the pyriform-amygdaloid complex in the cat. Certainly, these rather gross differences in observed emotional changes (presumably related to what appear to be only minor variations in the anatomical substrate involved in these somewhat conflicting studies) may serve to point up even more sharply the delicately balanced relationships which characterize limbic system participation in affective processes.

At least one additional contribution of the Bard and Mountcastle research program, however, was to call attention to the somewhat complicated role of the cingulate gyrus in the elaboration of such obviously complex motivational-emotional behavior patterns. Although the removal of this juxtallocortical structure in neodecorticate preparations was observed to lower the rage threshold in their earlier experiments, these investigators found that cingulate ablation in otherwise intact cats tended to raise this threshold and produce emotionally less responsive animals (15). Indeed, several authors (151, 350, 381) have referred to similar consequences of cingulectomy ('loss of fear,' 'social indifference') in an attempt to define the role of this juxtallocortical portion of the limbic system in emotional behavior, and although Pribram & Fulton (310) have emphasized the rather limited extent and duration of such changes, their observations generally confirm the character and direction of these effects.

Undoubtedly, however, what has now come to be known as the 'Klüver-Bucy syndrome' (363) appears to have suggested the most stimulating lead for a host of subsequent research efforts to unravel the somewhat complicated role of limbic system components in the elaboration of emotional behavior. In a paper presented to the American Neurological Association in 1949, for example, Fulton and his colleagues (137) reported that bilateral ablation of the frontotemporal portion of the juxtallocortex in monkeys can produce alterations in emotional behavior similar to, but apparently not as extensive as, those found by Klüver and Bucy following temporal neocortical and paleocortical lesions. Compulsive oral behavior and apparent lack of emotional responsiveness to aversive stimuli were observed in these frontotemporal preparations, but no alterations in sexual behavior seem to have appeared. As a matter of fact, the affective character of such changes are of an even more limited scope when the lesions are restricted to the lateral surface of the temporal lobe and preoccipital cortex, although Blum *et al.* (29) have observed following such lesions in monkeys some deficits in complex visual tasks and learned discriminative performance which they believe to be at least somewhat related to motivational-emotional effects.

When, however, experimental lesions are carefully restricted to the pyriform lobe, amygdaloid complex and hippocampus (sparing neocortical regions for the most part) in the monkey, Smith (351) has confirmed the appearance of very striking portions of the Klüver-Bucy syndrome (loss of 'fear' and 'anger' responses, docility, compulsive oral behavior) without gross motor or sensory deficits. In addition, this same report would seem to indicate that the docility and loss of fear can be produced in such animals without the compulsive oral behavior by selectively

ablating specific components of this 'pyriform-amygdaloid-hippocampal complex,' although the precise delimitation of these particular structures has not as yet been satisfactorily accomplished. Indeed, a number of subsequent studies with monkeys have succeeded in demonstrating varying portions of the Klüver-Bucy complex as a function of equally varied placements of limbic system lesions. Thompson & Walker (365, 377), for example, have confirmed the 'taming' effects of bilateral lesions of the medial surface of the temporal lobe apparently restricted to the amygdaloid complex and hippocampus, although they have emphasized the temporary character of such changes (4 to 5 month duration) and affirm the fact that lesions in other parts of the inferior temporal cortex do not produce these effects. Apart from this increased docility and reduction in 'fear' responsiveness (all these animals could still express 'anger' and 'rage' to appropriate stimuli), as well as a somewhat surprising decrease in sexual activity, however, none of the other Klüver-Bucy symptoms could be demonstrated, even though histological analysis of their data seemed to support the implication that the amygdala is primarily involved in the changes resulting from such lesions. Poirer (306) has also reported finding fragments of the Klüver-Bucy syndrome in monkeys with somewhat more restricted lesions of the temporal pole, although these observations have been limited largely to the apparent 'apathy' and 'drowsiness' of the operated animals without mention of other behavioral changes.

Significantly, continuing attempts to analyze the specific relationships in this temporal lobe-amygdala-hippocampus syndrome have led investigators to a wide variety of different animal species in their quest for some basic understanding of this rather complex motivational-emotional phenomenon. Pribram, Mishkin and their collaborators (130, 283, 284, 309, 312), for example, have reported upon the effects of lesions involving the frontotemporal cortex, temporal pole and amygdaloid complex in baboons and dogs, the results confirming, for the most part, the 'taming' and oral effects which follow involvement of these structures. And Schreiner & Kling (332, 334) have described similar behavioral changes associated with the amygdaloid complex and pyriform lobe in cats, agoutis and lynx. In the cat preparations (which were most extensively studied), refractoriness to rage- or anger-producing stimuli, exaggerated oral and vocal behavior, and marked hypersexuality were observed, a complex of changes similarly reported by Gastaut and his co-workers (141, 288) following amygdala lesions in the cat. The most striking observation in the notably wild and intractable agoutis and lynx studied by Schreiner & Kling, however, was the dramatic conversion to virtually complete (if somewhat temporary in the case of the lynx, at least) docility following bilateral lesions in the amygdala and pyriform lobe.

It may be of some interest to note that at least the state of hypersexuality produced by amygdalectomy in Schreiner & Kling's cats can be abolished by castration and restored with substitution therapy (333), suggesting the role of important neuroendocrine relationships involving the limbic system in the elaboration of such motivational-emotional behavior patterns. Furthermore, these same authors (332) have also reported that the characteristically placid amygdalectomized cat can be readily converted into a 'vicious,' 'rageful' animal by additional superimposed lesions in the ventromedial nucleus of the hypothalamus. And, in fact, one of the first efforts to analyze quantitatively the behavioral effects of such limbic system lesions upon the acquisition and retention of a conditioned avoidance response by Brady *et al.* (55) involved many of these same amygdalectomized cats. The avoidance technique used in these experiments consisted of the animal's passage through an open doorway separating the two compartments of a conventional 'double-grill' box in response to the presentation of a 30-sec. conditioned clicker stimulus, thus terminating the clicker and avoiding the shocks which followed failure to respond within the 30-sec. stimulus interval. Acquisition of such a conditioned avoidance response was found to be significantly impaired in bilaterally amygdalectomized cats, although virtually identical lesions appeared to have little effect upon the retention of precisely the same avoidance behavior in cats conditioned prior to operation. Weiskrantz & Pribram (386–388) have also undertaken similar efforts to approach the 'temporal lobe problem' in this somewhat quantitative fashion, and correspondingly significant decrements were observed in conditioned avoidance behavior following bilateral lesions involving not only the amygdaloid complex in the monkey, but other portions of the limbic system as well (frontotemporal cortex, cingulate gyrus).

A considerably broader conception of limbic system participation in emotional behavior would seem to be reflected, however, in the host of clinical and experimental observations which continue to emerge from more recent psychological and physiological

analyses of affective processes. Not only has the conditioned behavior of the individual animal with limbic system involvement begun to come under careful scrutiny in specifically controlled testing situations, but even the integration of social behavior and its dependence upon these neural systems has now been explored. Rosvold *et al.* (321) observed that the effects of amydalectomy in eight male Rhesus monkeys generally changed their hierarchical position in a group-cage situation from dominant to submissive, even though they appeared somewhat more 'aggressive' when in individual cages. Certainly, the results of these experiments would seem to suggest that the postsurgical social environment and the length of time preoperative relationships have existed can be as important a consideration as differences in the extent and location of the lesion in evaluating the consequences of limbic system ablations for emotional behavior. And indeed, clinical reports of observations following temporal lobe and amygdaloid lesions in man by Terzian & Ore (363) and Sawa *et al.* (326) have emphasized this same diminution of 'social aggressiveness.' Gastaut and colleagues (144) have also pointed out that discharging lesions in these limbic system structures, as seen in psychomotor epilepsy, apparently produce a lowered 'rage' threshold since these patients frequently show violent temper outbursts in social situations. It may also be significant that Gastaut & Collomb (142) have observed a decrease in sexual behavior in these patients with irritative lesions of the temporal lobe-amygdala region, while Gastaut & Mileto (143) have further elaborated upon the disturbances in sexual behavior which follow involvement of the hippocampus in both human and animal cases of rabies.

Many physiological studies (4, 9, 68, 77, 78, 132, 141, 202–204, 221–226, 257, 260, 307, 311, 336, 381) in both animals and man, using chemical and electrical stimulation as well as electrical recording methods, have also demonstrated limbic system involvement in a wide variety of somatic and autonomic phenomena closely related to the broad range of behavioral activities conventionally associated with emotional expression. Significantly, it has been difficult to discern any clear-cut topographical organization for specific behavioral components, even though the observations of Kaada *et al.* (203) would seem to suggest that such delineation may be possible. For the most part, however, the striking features of such correlative data would seem to be the extensive overlap of all sorts of behavioral responses in their representation at this limbic system level (203, 221–226), and the remarkably broad spectrum of psychological activities in which these structures can be presumed to participate (132, 141, 202, 257, 311). Heath and his collaborators (169, 238) have even recently proposed extensive involvement of these specific neural systems in the elaboration of 'thought' and 'psychological awareness.' The intimate relationship of these limbic structures (particularly the amygdala) to the mechanisms of neuroendocrine integration has been convincingly demonstrated by both stimulation and ablation studies (166, 190, 223, 225, 267, 308, 327, 331–333). Finally, electrophysiological methods have continued to define the characteristic functional interrelationships within the limbic system and subcortical regions basically involved in the elaboration of emotional behavior (68, 118, 119, 153–155, 157, 241, 242). Of particular importance in this respect would seem to be the extensive studies of MacLean and his collaborators (255 260), and of Gloor (153–155), carefully delineating the limbic system role in affective processes.

Even with this host of clinical and experimental observations, and the rapidly accumulating body of anatomical, physiological and psychological information, however, no completely satisfactory integration of the limbic system with the necessarily broad range of central neural participants in emotional behavior has as yet emerged. There never has been any shortage of speculative efforts assigning specific functional roles to the various components of this anatomical complex, and a significant thread of similarity is indeed discernible among the many neurological hypotheses which have characterized the multidisciplinary theorizing in this area. Almost 30 years ago, for example, Herrick (175), on a comparative anatomical basis, suggested that the limbic system may serve as a nonspecific activator for all cortical activities, influencing "the internal apparatus of general bodily attitude, disposition, and affective tone." Even Kleist's (215) speculations of the same era about the 'inner brain,' as he referred to the more medial aspects of the hemisphere, can be seen to emphasize the fact that these limbic structures were not only basic for 'emotional behavior,' 'attitudes' and 'drives,' but were also instrumental in correlating 'visceral receptions' from the oral, anal and genital regions, as well as the intestines, thus subserving functions related to the search for food and sexual objects. And clinical observations of human patients with limbic system involvement led

Grunthal (161) to propose that the hippocampus, as the virtual 'hub' of the limbic system, may represent a 'catalytic activator' which, although not necessarily participating in specialized functions itself, is nevertheless basic for the proper functioning of affective and neocortical activity.

More recently, MacLean (255) has reviewed and elaborated Papez' (302) earlier theoretical views on emotional behavior and limbic system mechanisms (or 'visceral brain,' as is MacLean's reference), suggesting the basic importance of these forebrain structures not only for affective processes, but also for correlating 'oral and visceral sensations' as well as 'impressions from the sex organs, body wall, eye and ear.' Even Pribram & Kruger (311) in their comprehensive review of the 'olfactory brain,' have speculatively assigned 'olfactory-gustatory,' 'metabolic' and 'socioemotional' functions to the various 'limbic' components comprising their three 'systems.' And Gloor's (155) recent analysis of telencephalic influences upon the hypothalamus has assigned to the limbic system the role of "modulator of functional patterns integrated at the level of the hypothalamus and the brain stem tegmentum," even though in his view, "the limbic system does not fundamentally integrate the functions it is capable of influencing by its activity." Indeed, the weight of available anatomical, physiological and psychological evidence would certainly seem to support at least some generally similar concept of the 'intermediary' role of the limbic system in the integration of brain-stem and neocortical participation in emotional behavior.

### *Neocortical Function*

Despite this recent experimental and theoretical emphasis upon limbic system relationships, however, the long-enduring quest for 'localized functions' at the level of the neocortex continues to exert important influences upon both clinical and laboratory contributions to the neurophysiological analysis of emotional behavior. For the most part, attention has traditionally focused upon the frontal lobes with specific reference to affective processes (83, 117, 126, 131, 132, 171, 200, 214, 231, 233, 244, 278, 279, 361, 366, 376, 382), although some additional concern with the participant role of more extensive neocortical regions (7, 86, 158, 212, 227, 282, 293, 304, 313) has recently been in evidence. Understandably, clinical observations can be seen to have contributed the lion's share to the available literature in this area, although the laboratory analysis of ablation consequences and selective changes in electrically recorded potentials from the neocortex has more recently suggested important neural-behavioral relationships. Long before systematic treatment of such problems was fashionable observations on the behavioral consequences of the 'sacred disease'—epilepsy—included both literary and professional descriptions of affective changes presumably related to neocortical involvement. And as early as 1875, David Ferrier (120) provided a provocative description of behavioral changes closely related to emotional phenomena in monkeys following experimental frontal ablations. Somewhat later, Bianchi (25) made similar observations, and the story of the classic report by Fulton & Jacobsen (136) before the London meetings of the Second International Neurological Congress in 1935 and the subsequent adoption of frontal ablations as a therapeutic procedure by Moniz & Lima (287) is now too well known to require detailed repetition.

Significantly, the presumed therapeutic emotional changes observed to follow such prefrontal lesions have frequently been rationalized in terms of the intimate anatomical and functional relationship of these more or less specific portions of the cerebral mantle with the affective integrative mechanisms of the diencephalon (via principally the dorsomedial thalamus). It has now become abundantly clear, however, that extensive limbic system influences doubtless exert important mediating effects on such diencephaliconeocortical interactions, and that the assessment of emotional changes consequent upon neocortical involvement must be considered within this integrative relational framework. Indeed, the wide variety of behavioral changes which have been observed to follow such frontal neocortical ablations would appear comprehensible only within the broad framework of such an integrative analysis. For the most part, the consequences of frontal lobe lesions appear to involve changes in the direction of diminished 'emotional responsiveness.' Both clinical and laboratory reports, however, have also confirmed the frequent appearance of increased 'emotional lability' in man and animal following at least some therapeutic and investigative efforts to alter affective behavior patterns with frontal neocortical ablation. Clearly we are a considerable distance from a satisfactory understanding of the participant role of such specific neocortical regions in the elaboration of emotional processes, although the evidence for such involvement seems unequivocal.

An important recent emphasis upon electroencephalographic studies in relation to 'affective states' can also be seen to hold considerable promise for a more thorough understanding of neocortical functions in emotional behavior. Only within the past decade have the first systematic treatments of this neurophysiological approach by Lindsley (247) and Darrow (90) begun to appear although, as we have already seen, even earlier explorations of EEG phenomena had suggested their relationship to the 'emotions' (22, 160, 189, 364, 397). Characteristically, changes in the EEG pattern "under conditions involving some degree of emotional arousal, as in apprehension, unexpected sensory stimulation, and anxiety states," as summarized by Lindsley (247) in his 1948 review, can be reflected in "a reduction or suppression of alpha rhythm and an increase in the amount of beta-like fast activity." Although the observations which provided the basis for these general conclusions did not focus upon any selective neocortical regions in particular, they can be seen to form at least part of the foundation for Lindsley's 'activation theory' of emotion (248) with its emphasis upon neocortical arousal in affective processes. Subsequent reports by Ulett *et al.* (370–372) and others (18, 23, 30, 91, 92, 113, 220), however, have suggested involvement of more specific cortical areas, and Walter (379) has even recently reported that emotional disturbances arising during flicker stimulation experiments can be associated with rather selective EEG changes in the temporal neocortex. Certainly, the close anatomical and functional association of the temporal lobes with limbic system structures intimately involved with the elaboration of emotional behavior would seem to fit well with such a suggested delineation of neocortical participation in affective processes.

## SOME RECENT DEVELOPMENTS

Probably the most striking feature of this long-enduring neurophysiological interest in the problem of emotion has been the slow pace at which experimental analysis of the critical behavioral phenomena has proceeded. Needless to say, this failure of psychological science to keep abreast of anatomical and physiological developments is clearly reflected in the obviously primitive, phenomenological and conspicuously prescientific descriptions and definitions of emotional behavior which can be seen to characterize most of the research in this area. And indeed, one cannot help but wonder about the economy and parsimony of elaborate speculative efforts to develop a comprehensive neurophysiological theory of emotion in the absence of a sound behavioristic account of those presumably affective interaction processes between organism and environment. The analysis of such functional relationships at this descriptive behavioristic level must provide the foundation for any adequate treatment of neurophysiological participation in 'emotional' events.

Within recent years, however, the emerging outlines of an objective psychological science have begun to provide precise and reliable techniques for controlling the behavior of the individual subject as a basis for interdisciplinary neurophysiological analysis. For the most part, the dedication of B. F. Skinner, his co-workers and others to the experimental analysis of behavior in its own right has been responsible for the development of these methods in a variety of applications and for their recent extension to the investigation of the problem which provides the subject matter for this chapter (6, 28, 31–44, 47–54, 56, 57, 101–103, 114–116, 121, 122, 145, 162, 177, 178, 185, 192–195, 209, 240, 252, 268, 269, 289, 290, 339–342, 345–348, 359, 373, 374, 388, 398).

The application of these so-called 'operant conditioning' techniques to the experimental analysis of both behavioral and neurophysiological problems can be seen to rest upon a simple principle, namely that the characteristics of an organism's behavior are, to a considerable extent at least, determined by what the environmental consequences of that behavior have been in the past. Thus the term 'operant behavior' has been used to refer to behavior which operates upon the environment in this fashion, and the process of manipulating such behavior as a function of its environmental consequences has been termed 'operant conditioning' (345). The systematic analysis of orderly relations among behavior segments within this framework has been accomplished, first, by selecting for measurement and manipulation a response having a topography congenial to the organism, and one that the organism can perform and immediately be in a position to repeat. Secondly, this kind of analysis has been enhanced by selecting an environmental consequence, or 'reinforcement,' that is appropriate to the particular individual and by utilizing motivational levels that are strong enough to minimize the effects of many experimentally irrelevant variables. Finally, an additional aspect of this approach to behavior science is the systematic limitation of the experimental environ-

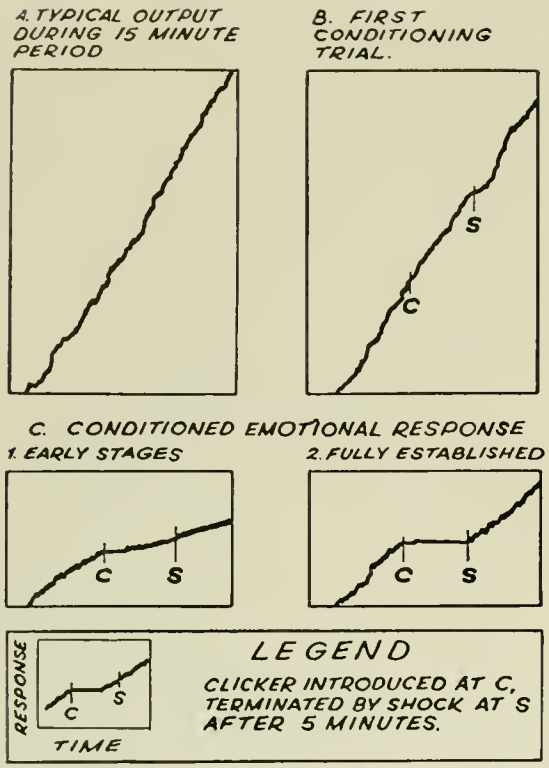



FIG. 2. The conditioned emotional response as it appears typically in the cumulative response curve. *Abscissae*, time; *ordinates*, cumulative number of responses. [From Hunt & Brady (193).]

ment to permit at least some reasonable degree of stimulus control and specification. Typically, the subject in such a study may be a hungry pigeon pecking at a lighted spot on the wall for a small amount of grain as reinforcement; or a thirsty rat may press a lever to obtain a small drop of water; or a monkey may push a panel in order to postpone a painful electric shock; or even *Homo sapiens* may pull a plunger to acquire a candy or cigarette reward. The point, of course, is not the investigation of eating, drinking or smoking behavior per se, or even of pain. Most importantly, the object of these techniques is to place some arbitrary sample of behavior under experimental control so that behaviorial processes may be investigated as a function of a wide variety of operations, including neurophysiological manipulations and even 'emotional' disturbance.

Estes & Skinner (116) first suggested the basis of an approach to at least one aspect of the 'emotion' problem within the framework of this developing behavior science, and several recent extensions of these methods to both the psychological and physiological analysis of affective processes (32, 36–41, 43–47, 51, 53, 54, 193, 194, 252, 268, 269, 290, 339, 341, 348) justify their enthusiastic acceptance by a broad interdisciplinary audience. Much of this work has had its origin in the rather common clinical and experimental observation that 'emotional' disturbance can, as one of several possible effects, disrupt or interfere with an organism's ongoing behavior. Experimentally, the fundamental empirical fact which has provided the cornerstone for such an approach to the problem of emotion is the suppressing effect of anticipated pain upon an animal's ongoing lever pressing behavior. This conditioned suppression phenomenon is readily produced by pairing some previously neutral stimulus with pain shock. The typical consequences of such a procedure in the rat (involving repeated presentations of a clicking noise for 5 min. followed by pain shock to the feet during a lever pressing session for water reward) are shown in figure 2 (193). The clicking noise is introduced at point *C* on the cumulative lever pressing curves, continues for 5 min. and is terminated continguously with shock at point *S*. Within a few trials, the anticipatory 'emotional' response to the clicker begins to appear as a perturbation in the lever pressing curve, accompanied by crouching, immobility and usually defecation.

Now this emphasis upon a rather primitive and possibly somewhat molecular psychological phenomenon as the starting point for an experimental analysis of emotional behavior has several clear-cut advantages from the standpoint of a neurophysiological analysis. First, focus directly upon this conditioned suppression response per se eliminates a major source of error attributable to variables that affect the instrumental behavior from which 'emotional' effects are usually inferred in the more conventional observational or even 'escape-avoidance' learning approach to this problem. Secondly, this simple relatively uncomplicated response is elicitable under a wide range of conditions and appears in quite consistent form or topography in all animals. Thirdly, this response is remarkably stable over time, surviving without apparent diminution in the absence of exercise or further reinforcement virtually throughout the entire life span of the organism. Finally, and probably most importantly from the standpoint of a relational neurophysiological analysis, the technique of superimposing the emotional response upon a well-established stable lever-pressing habit makes it possible to approximate

an objectively quantifiable definition of the behavior in terms of changes in output during various segments of the lever pressing curve (195). In many respects, this rather restricted behavior sample appears to be prototypical of the most primitive aspects of an organism's emotional repertoire, and the investigation of its vicissitudes—the conditions which determine its increases and decreases in strength, etc.—has already contributed significantly to the differential experimental analysis of both the physiological and psychological variables upon which the organization of emotional behavior depends.

The potential implications for a neurophysiological analysis of emotional behavior within this rather broad operant conditioning framework first became apparent as a consequence of a series of studies on the effects of electroconvulsive shock (33, 34, 49, 50, 52, 54, 56, 145, 193, 195). The results of these experiments showed that it was possible to separate and measure selectively the effects of such physiological manipulations upon the 'emotional' components of a behavior segment independently of any gross effects upon the simple repetitive lever-pressing habit which provided the control base line. Subsequent applications of this approach to the analysis of more direct neurophysiological participation in affective processes have made it possible to show, for example, that the elaboration of even such basic aspects of emotional behavior depends heavily upon the integrity of quite specific portions of the forebrain and brain stem, notably the limbic system. Although large neocortical lesions were found to produce little or no effect upon the acquisition, retention or extinction of the conditioned suppression pattern, lesions in the septal region and hippocampus produced significant decrements in the maintenance of such behavior and most dramatic changes in gross affective expression (36, 53). In addition, lesions of the habenular complex of the thalamus appear to reduce resistance to extinction of the conditioned suppression response, although cingulate lesions have no apparent effect on such behavior (40, 43, 54).

More recently, this operant conditioning approach to the neurophysiological analysis of emotional behavior has found most dramatic application in the exploration of reinforcement or 'reward' effects produced by intracranial electrical self-stimulation of the nervous system. Olds & Milner (301) first reported that rats, electrically stimulating themselves in various portions of the limbic system by pressing a

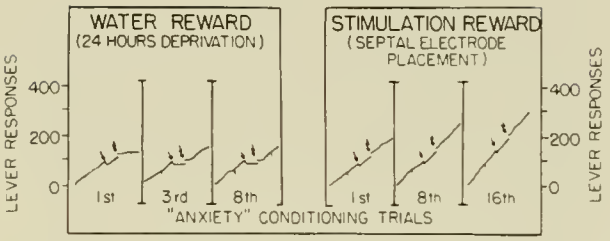



FIG. 3. Sample cumulative response curves showing acquisition trials for the conditioned 'anxiety' response superimposed upon lever pressing for water and intracranial electrical stimulation reward. The *oblique solid arrows* indicate the onset of the conditioned auditory stimulus, and the *oblique broken arrows* indicate the termination of the conditioned stimulus contiguously with the brief unconditioned grid-shock stimulus to the feet during each trial. [From Brady (45).]

bar, would maintain high lever-pressing rates over long periods of time without any other reward. This same phenomenon has been systematically reproduced and analyzed in the cat and monkey by Brady (44, 46) and others (246, 342), and investigative efforts have begun to delimit some of the critical variables in this area. The specific anatomical locus of the stimulating electrodes, schedules of intracranial electrical stimulation reinforcement, food and water deprivation, stimulus intensity, temporal factors, and the like have all been shown to constitute critical determinants of this effect (44, 45, 46, 48, 299, 300, 342).

Of particular interest from the standpoint of a primary concern with neurophysiological relationships and emotional behavior, however, would seem to be the recent demonstration of interaction effects between the conditioned suppression response illustrated in figure 2 and this intracranial self-stimulation phenomenon (40, 44, 45, 46). The consequences of repeated pairings of the clicker and shock according to this conditioning procedure have been consistently reported to include suppression of the lever-pressing rate, crouching, immobility and usually defecation in response to presentation of the auditory stimulus. Although this relatively stable conditioned 'fear' pattern was reported by Brady (40, 43–46) to be readily elicited by presentation of the clicker when both rats and monkeys were pressing a lever for food or water reward, substitution of brain stimulation through chronically implanted limbic system electrodes (septal region, medial forebrain bundle) for the food or water on the same reinforcement schedule resulted in failure of the auditory

stimulus to elicit the emotional suppression of lever-pressing behavior. Figure 3 shows the development of the conditioned 'fear' response in a rat with repeated pairings of clicker and shock superimposed upon the water-reinforced lever-pressing curve, and illustrates the striking failure of the suppression behavior to appear in the same animal with the same clicker and shock when lever pressing is rewarded with brain stimulation in the septal region rather than water. With the monkey, this same phenomenon has been demonstrated with the self-stimulation electrodes in the anterior forebrain portions of the limbic system (medial forebrain bundle), although an extensive analysis of rewarding electrode placements which do not show this interaction effect with the conditioned emotional response has not yet been accomplished.

It is clear that even this developing refinement in the experimental analysis of neuropsychological relationships has not as yet provided more than the most preliminary framework within which a satisfactory formulation of emotional behavior is to be sought. An almost infinite complexity remains to be unraveled at the level of organismic-environmental interactions, and an adequate neurophysiological analysis of affective processes would seem to bear a critical dependence upon the systematization of such behavioral relationships per se. Indeed, many attempts have been made to order these behavioral diversities to single broad principles within the context of contemporary psychological emphasis upon 'acquired drives' and similar motivational constructs. And physiological focus upon specific 'neural mechanisms' in speculative accounts of the emotion problem has at times appeared equally restrictive. The promise of a more empirical relational analysis of independently definable psychological and physiological events, however, may be seen to reflect some concern that such monolithic ordering, prematurely embraced, might serve to obscure important neurobehavioral relationships basic to an understanding of what we conventionally regard as emotion.

## REFERENCES


1. Alpers, B. J. *A.M.A. Arch. Neurol. & Psychiat.* 38: 291, 1937.
2. Anand, B. K. and J. R. Brobeck. *Yale J. Biol. & Med.* 24: 132, 1951.
3. Arnold, M. B. In: *Feelings and Emotions*, edited by M. L. Reymert. New York: McGraw-Hill, 1950, p. 11.
4. Austt, E. G., R. Arana, E. Migliaro, M. Sande and J. Segundo. *Electroencephalog. & Clin. Neurophysiol.* 6: 653, 1954.
5. Ax, A. F. *Psychosom. Med.* 15: 433, 1953.
6. Azrin, N. H. *J. Psychol.* 42: 3, 1956.
7. Bailey, P. and F. A. Gibbs. *J.A.M.A.* 145: 365, 1951.
8. Baird, H. N., B. Gudetti, V. Reyes, H. T. Wycis and E. G. Spiegel. *Fed. Proc.* 10: 8, 1951.
9. Baldwin, M., L. Frost and C. Wood. *Neurology* 4: 486, 1954.
10. Bard, P. *Am. J. Physiol.* 84: 490, 1928.
11. Bard, P. *Psychol. Rev.* 41: 309, 424, 1934.
12. Bard, P. In: *Handbook of General Experimental Psychology*, edited by C. Murchison. Worcester: Clark Univ. Press, 1934, p. 264.
13. Bard, P. In: *The Inter-Relationship of Mind and Body*, edited by A. Frantz. Baltimore: Williams & Wilkins, 1939, p. 190.
14. Bard, P. In: *The Hypothalamus and Central Levels of Autonomic Function*, edited by J. Fulton. Baltimore: Williams & Wilkins, 1940, p. 551.
15. Bard, P. In: *Feelings and Emotions*, edited by M. L. Reymert. New York: McGraw-Hill, 1950, p. 211.
16. Bard, P. and V. B. Mountcastle. In: *The Frontal Lobes*, edited by J. Fulton. Baltimore: Williams & Wilkins, 1948, p. 362.
17. Bard, P. and D. M. Rioch. *Bull. Johns Hopkins Hosp.* 60: 73, 1937.
18. Barker, W., S. Burgwin and D. J. Simons. *J. Nerv. & Ment. Dis.* 112: 187, 1950.
19. Bazett, H. C. and W. G. Penfield. *Brain* 45: 185, 1922.
20. Beebe-Center, J. G. *The Psychology of Pleasantness and Unpleasantness*. New York: Van Nostrand, 1932.
21. Bender, W. R. G. *Psychol. Monogr.* 44: 1, 1933.
22. Berger, H. *Arch. Psychiat.* 87: 527, 1929.
23. Berlin, I. N. and C. L. Yeager. *Am. J. Dis. Child.* 81: 664, 1951.
24. Berrien, F. K. *J. Exper. Psychol.* 24: 485, 1939.
25. Bianchi, L. *The Mechanism of the Brain and the Function of the Frontal Lobes*, translated by J. H. MacDonald. New York: Wood, 1922.
26. Bindra, D. *Canad. J. Psychol.* 9: 161, 1955.
27. Bindra, D. and W. R. Thompson. *J. Comp. & Physiol. Psychol.* 46: 43, 1953.
28. Blough, D. S. *Science* 121: 703, 1955.
29. Blum, J. S., K. L. Chow and K. H. Pribram. *J. Comp. Neurol.* 93: 53, 1950.
30. Bonvallet, M., P. Dell and G. Hiebel. *Electroencephalog. & Clin. Neurophysiol.* 6: 119, 1954.
31. Boren, J. J. *J. Pharmacol. & Exper. Therap.* 119: 134, 1957.
32. Boren, J. J. and M. Sidman. *Canad. J. Psychol.* 11: 185, 1957.
33. Brady, J. V. *J. Comp. & Physiol. Psychol.* 44: 507, 1951.
34. Brady, J. V. *J. Comp. & Physiol. Psychol.* 45: 9, 1952.
35. Brady, J. V. *J. Comp. & Physiol. Psychol.* 46: 307, 1953.
36. Brady, J. V. *XIV Internat. Congr. Plychol., Proc.* Amsterdam: North-Holland, 1954, p. 148.
37. Brady, J. V. *J. Psychol.* 40: 25, 1955.
38. Brady, J. V. *Science* 123: 1033, 1956.
39. Brady, J. V. *Ann. New York Acad. Sc.* 64: 632, 1956.
40. Brady, J. V. *Tr. New York Acad. Sc.* 18: 601, 1956.

41. Brady, J. V. In: *Brain Mechanisms and Drug Action*, edited by W. S. Fields. Springfield: Thomas, 1957, p. 111.
42. Brady, J. V. *Ann. New York Acad. Sc.* 66: 719, 1957.
43. Brady, J. V. In: *Experimental Psychopathology*, edited by P. Hoch and J. Zubin. New York: Grune, 1957, p. 20.
44. Brady, J. V. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 689.
45. Brady, J. V. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 193.
46. Brady, J. V. In: *Electrical Stimulation of the Brain. Subcortical Integrative System*, edited by D. Scheer and D. C. Kroeger. Austin: Univ. Texas Press, 1960.
47. Brady, J. V. *Psychopharmacology: Problems in Evaluation*, edited by J. O. Cole and R. W. Gerard. Nat. Acad. Sc.–Nat. Res. Council Publ. 583, Washington, 1959.
48. Brady, J. V., J. Boren, D. Conrad and M. Sidman. *J. Comp. & Physiol. Psychol.* 50: 134, 1957.
49. Brady, J. V. and H. F. Hunt. *J. Comp. & Physiol. Psychol.* 44: 204, 1951.
50. Brady, J. V. and H. F. Hunt. *J. Comp. & Physiol. Psychol.* 45: 180, 1952.
51. Brady, J. V. and H. F. Hunt. *J. Psychol.* 40: 313, 1955.
52. Brady, J. V., H. F. Hunt and I. Geller. *J. Comp. & Physiol. Psychol.* 47: 454, 1954.
53. Brady, J. V. and W. J. H. Nauta. *J. Comp. & Physiol. Psychol.* 46: 339, 1953.
54. Brady, J. V. and W. J. H. Nauta. *J. Comp. & Physiol. Psychol.* 48: 412, 1955.
55. Brady, J. V., L. Schreiner, I. Geller and A. Kling. *J. Comp. & Physiol. Psychol.* 49: 381, 1956.
56. Brady, J. V., W. C. Stebbins and R. Galambos. *J. Comp. & Physiol. Psychol.* 46: 363, 1953.
57. Brady, J. V., W. C. Stebbins, and H. F. Hunt. *J. Comp. & Physiol. Psychol.* 46: 368, 1953.
58. Brobeck, J. R., J. Tepperman and C. N. Long. *Yale J. Biol. & Med.* 15: 831, 1943.
59. Broca, P. *Rev. Anthropol.* 1: 385, 1878.
60. Broca, P. *Rev. Anthropol.* 2: 385, 1879.
61. Bromiley, R. B. *J. Comp. & Physiol. Psychol.* 41: 102, 1948.
62. Brookhart, J. M. and F. L. Dey. *Am. J. Physiol.* 133: 551, 1941.
63. Brookhart, J. M., F. L. Dey and S. W. Ranson. *Endocrinology* 28: 561, 1941.
64. Brooks, C. M. *New Zealand M. J.* 46: 243, 1947.
65. Brothers, J. D. *Genet. Psychol. Monogr.* 53: 75, 1956.
66. Brower, D. *J. Gen. Psychol.* 34: 47, 1946.
67. Brown, S. and E. A. Schäfer. *Phil. Trans. B* 179: 303, 1888.
68. Cadilhac, J. *Hippocampe et Epilepsie*. Montepellier: Dehan, 1955.
69. Cannon, W. B. *Am. J. Psychol.* 39: 106, 1927.
70. Cannon, W. B. *Bodily Changes in Pain, Hunger, Fear and Rage*. New York: Appleton, 1929.
71. Cannon, W B. *Lancet* 218: 1109, 1930.
72. Cannon, W. B. *Psychol. Rev.* 38: 281, 1931.
73. Cannon, W. B. and S. W. Britton. *Am. J. Physiol.* 72: 283, 1925.
74. Cannon, W. B., H. F. Newton, E. M. Bright, V. Menkin and R. M. Moore. *Am. J. Physiol.* 89: 84, 1929.
75. Cannon, W. B. and A. Rosenblueth. *Autonomic Neuro-Effector Systems*. New York: Macmillan, 1937.
76. Cannon, W. B. and A. Rosenblueth. *The Supersensitivity of Denervated Structures: A Law of Denervation*. New York: Macmillan, 1949.
77. Chapman, W. P., H. R. Schroeder, G. Geyer, M. Brazier, C. Fager, J. Poppen, H. Solomon and P. Yakovlev. *Science* 120: 949, 1954.
78. Chapman, W. P., H. Solomon, H. Schroeder, M. Brazier, G. Geyer, C. Fager, J. Poppen and P. Yakovlev. *III Internat. Congr. Intern. Med.*, Proc. Uppsala: Almqvist, 1956, p. 66.
79. Chow, K. L. *A.M.A. Arch. Neurol. & Psychiat.* 71: 762, 1954.
80. Clark, W. E. LeGros, J. Beattie, G. Riddoch and N. M. Dott. *The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects*. Edinburgh: Oliver, 1938.
81. Clark, W. E. and M. Meyer. *Brain* 70: 304, 1947.
82. Claude, H. and J. Lhermitte. *Presse méd.* 25: 417, 1917.
83. Cobb, S. In: *Personality and the Behavior Disorders*, edited by J. Hunt. New York: Ronald, 1944, p. 550.
84. Courts, F. A. *Psychol. Bull.* 39: 347, 1942.
85. Cox, L. B. *Tumours of the Brain: Their Relation to Pathological Sleep and other Changes in the Conscious State*. M. H. Australia, 1937.
86. Critchley, M. *The Parietal Lobes*. Baltimore: Williams & Wilkins, 1953.
87. Cushing, H. *Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System*. Springfield: Thomas, 1932.
88. Darrow, C. W. *Psychol. Bull.* 33: 73, 1936.
89. Darrow, C. W. *Physiol. Rev.* 23: 1, 1943.
90. Darrow, C. W. In: *Feelings and Emotions*, edited by M. L. Reymert. New York: McGraw-Hill, 1950, p. 247.
91. Darrow, C. W. *Comp. Psychol. Monogr.* 20: 51, 1950.
92. Darrow, C. W. *Ann. New York Acad. Sc.* 56: 289, 1953.
93. Darwin, C. *The Expression of the Emotions in Man and Animals*. London: John Murray, 1872.
94. Davis, R. C. *J. Exper. Psychol.* 23: 141, 1938.
95. Davis, R. C. In: *Methods of Psychology*, edited by T. G. Andrews. New York: Wiley, 1948, p. 391.
96. Delafresnaye, J. F. (editor). *Brain Mechanisms and Consciousness*. Oxford: Blackwell, 1954.
97. Delay, J., B. Laine, J. Puech and J. Clavreul. *Encéphale* 4: 289, 1953.
98. Delgado, J. M. R. *Yale J. Biol. & Med.* 24: 351, 1952.
99. Delgado, J. M. R. *J. Neurophysiol.* 18: 261, 1955.
100. Delgado, J. M. R., W. W. Roberts and N. E. Miller. *Am. J. Physiol.* 179: 587, 1954.
101. Dews, P. B. *J. Pharmacol. & Exper. Therap.* 113: 393, 1955.
102. Dews, P. B. *J. Pharmacol. & Exper. Therap.* 115: 380, 1955.
103. Dews, P. B. *Ann. New York Acad. Sc.* 65: 268, 1956.
104. Diethelm, O. *A.M.A. Arch. Neurol. & Psychiat.* 36: 342, 1936.
105. Diethelm, O., E. J. Doty and A. T. Milhorat. *A.M.A. Arch. Neurol. & Psychiat.* 54: 110, 1945.
106. Dinsmoor, J. A. *Psychol. Rev.* 61: 34, 1954.
107. Dinsmoor, J. A. *Psychol. Rev.* 62: 96, 1955.
108. Dollard, J., L. W. Doob, N. E. Miller, O. H. Mowrer

AND R. R. SEARS. *Frustration and Aggression*. New Haven: Yale Univ. Press, 1939.
109. DUFFY, E. *J. Gen. Psychol.* 25: 283, 1941.
110. DUNBAR, H. F. *Emotions and Bodily Changes* (4th ed.). New York: Columbia, 1954.
111. DUNLAP, K. (editor). *The Emotions*. Baltimore: Williams & Wilkins, 1922.
112. DUSSER DE BARENNE, H. G. *Arch. neerl. Physiol.* 4: 31, 1920.
113. ELLINGSON, R. J. *Psychol. Bull.* 53: 1, 1956.
114. ESTES, W. K. *Psychol. Monogr.* 57: No. 263, 1944.
115. ESTES, W. K. *J. Exper. Psychol.* 38: 173, 1948.
116. ESTES, W. K. AND B. F. SKINNER. *J. Exper. Psychol.* 29: 390, 1941.
117. EVARTS, E. V. AND H. W. NISSEN. *A.M.A. Arch. Neurol. & Psychiat.* 69: 323, 1953.
118. FAURE, M. J. AND M. PORTMANN. *Rev. laryng.* 76: 168, 1955.
119. FEINDEL, W. AND P. GLOOR. *Electroencephalog. & Clin. Neurophysiol.* 6: 389, 1954.
120. FERRIER, D. *Phil. Trans.* 165: 433, 1875.
121. FERSTER, C. B. *Psychol. Bull.* 50: 264, 1953.
122. FERSTER, C. B. AND B. F. SKINNER. *Schedules of Reinforcement*. New York: Appleton, 1957.
123. FINESINGER, J. E. *Am. J. Psychiat.* 100: 659, 1944.
124. FOERSTER, O. AND O. GAGEL. *Ztschr. ges. Neurol. Psychiat.* 149: 312, 1933.
125. FOX, C. A., W. A. MCKINLEY AND H. W. MAGOUN. *J. Neurophysiol.* 7: 1, 1944.
126. FREEMAN, W. AND J. W. WATTS. *Psychosurgery*. Springfield: Thomas, 1942.
127. FRENCH, J. D. AND H. W. MAGOUN. *A.M.A. Arch. Neurol. & Psychiat.* 68: 591, 1952.
128. FREUD, S. *Collected Papers*. London: Hogarth Press, 1924.
129. FRICK, F. C. *J. Comp. & Physiol. Psychol.* 46: 120, 1953.
130. FULLER, J. L., H. E. ROSVOLD AND K. H. PRIBRAM. *J. Comp. & Physiol. Psychol.* 50: 89, 1957.
131. FULTON, J. F. *The Frontal Lobes*. Baltimore: Williams & Wilkins, 1948.
132. FULTON, J. F. *Frontal Lobotomy and Affective Behavior*. New York: Norton, 1951.
133. FULTON, J. F. *Yale J. Biol. & Med.* 26: 107, 1953.
134. FULTON, J. F. AND P. BAILEY. *J. Nerv. & Ment. Dis.* 69: 145, 1929.
135. FULTON, J. F. AND F. D. INGRAM. *J. Physiol.* 67: 27, 1929.
136. FULTON, J. F. AND C. F. JACOBSEN. *Advances Mod. Biol. (U.S.S.R.)* 4: 113, 1935.
137. FULTON, J. F., K. H PRIBRAM, J. A. STEVENSON AND P. D. WALL. *Tr. Am. Neurol. A.* 74: 175, 1949.
138. GALAMBOS, R., G. SHEATZ AND V. G. VERNIER. *Science* 123: 376, 1956.
139. GANTT, W. H *Experimental Basis for Neurotic Behavior*. New York: Hoeber, 1944.
140. GASKILL, H. V. *Genet. Psychol. Monogr.* 14: 177, 1933.
141. GASTAUT, H. *J. physiol., Paris* 44: 431, 1952.
142. GASTAUT, H. AND H. COLLOMB. *Ann. méd.-psychol.* 2: 357, 1956.
143. GASTAUT, H. AND G. MILETO. *Rev. neurol.* 92: 5, 1955.
144. GASTAUT, H., G. MORIN AND N. LESEVRE. *Ann. méd.-psychol.* 1: 1, 1955.
145. GELLER, I., M SIDMAN AND J. V. BRADY. *J. Comp. & Physiol. Psychol.* 48 130, 1955.
146. GELLHORN, E. *Autonomic Regulations*. New York: Interscience, 1943.
147. GELLHORN, E. In: *Anxiety*, edited by P. Hoch and J. Zubin. New York: Grune, 1950, p. 205.
148. GELLHORN, E., R. CORTELL AND J. FELDMAN. *Science* 92: 288, 1940.
149. GILDEA, E. F., V. L. MAILHOUSE AND D. F. MORRIS. *Am. J. Psychiat.* 92: 115, 1935.
150. GLEES, P. *J. Neuropath. & Exper. Neurol.* 5: 54, 1946.
151. GLEES, P., J. COLE, M WHITTY AND H. CAIRNS. *J. Neurol. Neurosurg. & Psychiat.* 13: 178, 1950.
152. GLOOR, P. *A.M.A. Arch. Neurol. & Psychiat.* 71: 773, 1954.
153. GLOOR, P. *Electroencephalog. & Clin. Neurophysiol.* 7: 223, 1955.
154. GLOOR, P. *Electroencephalog. & Clin. Neurophysiol.* 7: 243, 1955.
155. GLOOR, P. In: *Hypothalamic-Hypophysial Interrelationships*, edited by W. S. Fields. Springfield: Thomas, 1956, p. 74.
156. GOLTZ, F. *Arch. ges. Physiol.* 51: 570, 1892.
157. GREEN, J. D. AND A. A. ARDUINI. *J. Neurophysiol.* 17: 533, 1954.
158. GREEN, J. R., R. E. H. DUISBERG AND W. B. MCGRATH. *J. Neurosurg.* 8: 157, 1951.
159. GRINKER, R. R. *Psychosom. Med.* 1: 19, 1939.
160. GRINKER, R. R. AND H. M. SERATA. *J. Neurophysiol.* 1: 573, 1938.
161. GRUNTHAL, E. *Monatsschr. Psychiat. u. Neurol.* 113: 1, 1945.
162. GUTTMAN, N. AND H. I. KALISH. *J. Exper. Psychol.* 51: 79, 1956.
163. HAGGARD, E. A. *J. Exper. Psychol.* 35: 46, 1945.
164. HARLOW, H. F. AND R. STAGNER. *Psychol. Rev.* 39: 570, 1932.
165. HARLOW, H. F. AND R. STAGNER. *Psychol. Rev.* 40: 184, 1933.
166. HARRIS, G. W. *Adrenal Cortex, Transactions of the Third Conference*. New York: Macy, 1952, p. 54.
167. HEAD, H. *Studies in Neurology*. London: Frawde, Hodder & Staughton, 1920.
168. HEATH, R. G. (editor). *Studies in Schizophrenia*. Cambridge: Harvard, 1954.
169. HEATH, R. G. *Psychosom. Med.* 5: 383, 1955.
170. HEATH, R. G. AND B. E. LEACH. In: *Changing Concepts in Psychoanalytic Medicine*, edited by S. Rado and G. Daniels. New York: Grune, 1956, p. 201.
171. HEBB, D. O. *A.M.A. Arch. Neurol. & Psychiat.* 54: 10, 1945.
172. HEBB, D. O. *Psychol. Rev.* 53: 88, 1946.
173. HEBB, D. O. *Psychol. Rev.* 53: 259, 1946.
174. HEBB, D. O. *The Organization of Behavior*. New York: Wiley, 1949.
175. HERRICK, C. J. *Proc. Nat. Acad. Sc., Washington* 19: 7, 1933.
176. HERRNSTEIN, R. J. AND W. H. MORSE. *Am. Psychologist* 11: 448, 1956.
177. HERRNSTEIN, R. J. AND W. H. MORSE. *Science* 124: 367, 1956.
178. HERRNSTEIN, R. J. AND W. H MORSE. *Science.* 125: 929, 1957.
179. HESS, W. R. *Ber. ges. Physiol.* 42: 554, 1928.
180. HESS, W. R. *Die Methodik der lokalisierten Reizung und Ausschaltung subkortikaler Hirnabschnitte*. Leipzig: Thieme, 1932.

181. Hess, W. R. *Das Zwischenhirn: Syndrome, Lokalisationen, Funktionen.* Basel: Schwabe, 1949.
182. Hess, W. R. *Diencephalon: Autonomic and Extrapyramidal Functions.* New York: Grune, 1954.
183. Hess, W. R. and K. Akert. *A.M.A. Arch. Neurol. & Psychiat.* 73: 127, 1955.
184. Hetherington, A. W. and S. W. Ranson. *Am. J. Physiol.* 136: 609, 1942.
185. Hill, H. E., R. E. Belleville and A. Wikler. *Science* 120: 153, 1954.
186. Hill, D. and G. Parr. *Electroencephalography.* New York: Macmillan, 1950.
187. Hinsey, J. C. In: *The Hypothalamus and Central Levels of Autonomic Function*, edited by J. Fulton. Baltimore: Williams & Wilkins, 1940, p. 657.
188. Hoagland, H. *J. Aviation Med.* 18: 450, 1947.
189. Hoagland, H., D. E. Cameron and M. A. Rubin. *J. Gen. Psychol.* 19: 227, 1938.
190. Hume, D. M. and G. J. Wittenstein. *Proceedings of the First ACTH Conference.* Philadelphia: Blakiston, 1950, p. 134.
191. Hunt, A. and C. Landis. *J. Exper. Psychol.* 19: 309, 1936.
192. Hunt, H. F. *Ann. New York Acad. Sc.* 65: 258, 1956.
193. Hunt, H. F. and J. V. Brady. *J. Comp. & Physiol. Psychol.* 44: 88, 1951.
194. Hunt, H. F. and J. V. Brady. *J. Comp. & Physiol. Psychol.* 48: 305, 1955.
195. Hunt, H. F., P. Jernberg and J. V. Brady. *J. Comp. & Physiol. Psychol.* 45: 589, 1952.
196. Hunt, W. A. In: *Foundations of Psychology*, edited by E. G. Boring, J. S. Langfeld and H. P. Weld. New York: Wiley, 1948.
197. Ingram, W. R. *Electroencephalog. & Clin. Neurophysiol.* 4: 397, 1952.
198. Ingram, W. R., R. W. Barris and S. W. Ranson. *A.M.A. Arch. Neurol. & Psychiat.* 35: 1175, 1936.
199. Ingram, W. R., J. R. Knott, M. D. Wheatley and T. D. Summers. *Electroencephalog. & Clin. Neurophysiol.* 3: 37, 1951.
200. Jacobsen, C. F. *Comp. Psychol. Monogr.* 13: No. 63, 1936.
201. James, W. *Mind* 9: 189, 1884.
202. Kaada, B. R. *Acta physiol. scandinav.* 183: 285, 1951.
203. Kaada, B. R., P. Andersen and J. Jansen. *Neurology* 4: 48, 1954.
204. Kaada, B. R., J. Jansen and P. Andersen. *Neurology* 3: 844, 1953.
205. Kantor, J. R. *Principles of Psychology.* New York: Knopf, 1924.
206. Kaplan, M. *J. Comp. & Physiol. Psychol.* 45: 538, 1952.
207. Karplus, J. P. In: *Handbuch der Neurologie*, edited by O. Bumke and O. Foerster. Berlin: Springer, 1937, p. 402.
208. Keller, A. D. *Am. J. Physiol.* 100: 576, 1932.
209. Keller, F. S. *Psychol. Rev.* 4: 235, 1941.
210. Keller, F. S. and W. N. Schoenfeld. *Principles of Psychology.* New York: Appleton, 1950.
211. Kelly, A. H., L. F. Beaton and H. W. Magoun. *J. Neurophysiol.* 9: 181, 1946.
212. Keschner, M., M. B. Bender and I. Strauss. *A.M.A. Arch. Neurol. & Psychiat.* 35: 572, 1936.
213. Kessler, M. M. *Proc. Soc. Exper. Biol. & Med.* 47: 225, 1941.
214. Klebanoff, S. G., J. L. Singer and H. Wilensky. *Psychol. Bull.* 51: 1, 1954.
215. Kleist, L. *Gehirnpathologie.* Leipzig: Barth, 1934.
216. Klüver, H. *Journal-Lancet* 72: 567, 1952.
217. Klüver, H. and P. C. Bucy. *Am. J. Physiol.* 119: 352, 1937.
218. Klüver, H. and P. Bucy. *J. Psychol.* 5: 33, 1938.
219. Klüver, H. and P. Bucy. *A.M.A. Arch. Neurol. & Psychiat.* 42: 979, 1939.
220. Knott, J. R. and R. E. Correll. *Electroencephalog. & Clin. Neurophysiol.* 6: 158, 1954.
221. Koikegami, H. and S. Fuse. *Folia psychiat. neurol. Japonica* 5: 188, 1952.
222. Koikegami, H. and S. Fuse. *Folia psychiat. neurol. Japonica* 6: 94, 1952.
223. Koikegami, H., S. Fuse, T. Yokoyama, T. Watanabe and H. Watanabe. *Folia psychiat. neurol. Japonica* 8: 336, 1955.
224. Koikegami, H., A. Kimoto and C. Kito. *Folia psychiat. neurol. Japonica* 7: 87, 1953.
225. Koikegami, H., T. Yamada and K. Usui. *Folia psychiat neurol. Japonica* 8: 7, 1954.
226. Koikegami, H. and Y. Yoshida. *Folia psychiat. neurol. Japonica* 7: 109, 1952.
227. Kolodny, A. *Brain* 51: 385, 1928.
228. Lacey, J. I. *Ann. New York Acad. Sc.* 67: 123, 1956.
229. Lacey, J. I., R. L. Smith and A. Green. *Psychosom. Med.* 17: 208, 1955.
230. Landis, C. In: *Handbook of General Experimental Psychology*, edited by C. Murchison. Worcester: Clark Univ. Press, 1934, p. 312.
231. Landis, C. *J. Nerv. & Ment. Dis.* 115: 203, 1952.
232. Landis, C. and W. A. Hunt. *Psychol. Rev.* 39: 467, 1932.
233. Lanois, C., J. Zubin and F. Mettler. *J. Psychol.* 30: 123, 1950.
234. Lange, C. G. *Om Sindsbevegelser.* Leipzig: Theodor Thomas, 1887.
235. Lashley, K. S. *Psychol. Rev.* 45: 42, 1938.
236. Lazarus, R. S., J. Deese and S. Osler. *Psychol. Bull.* 49: 293, 1952.
237. Leeper, R. W. *Psychol. Rev.* 55: 5, 1948.
238. Lesse, H., R. Heath, W. Mickel, R. Monroe and W. Miller. *J. Nerv. & Ment. Dis.* 122: 433, 1955.
239. Lhamon, W. T. *Psychosom. Med.* 11: 113, 1949.
240. Libby, A. *J. Exper. Psychol.* 42: 100, 1951.
241. Liberson, W. T. and K. Akert. *Electroencephalog. & Clin. Neurophysiol.* 7: 211, 1955.
242. Liberson, W. T. and J. Cadilhac. *Electroencephalog. & Clin. Neurophysiol.* 6: 710, 1954.
243. Lichtenstein, P. E. *J. Comp. & Physiol. Psychol.* 43: 16, 1950.
244. Lichtenstein, P. E. *J. Comp. & Physiol. Psychol.* 43: 419, 1950.
245. Liddell, H. S. *Emotional Hazards in Animals and Man.* Springfield: Thomas, 1956.
246. Lilly, J. C. *Science* 125: 748, 1957.
247. Lindsley, D. B. In: *Feelings and Emotions*, edited by M. L. Reymert. New York: McGraw-Hill, 1950, p. 238.
248. Linosley, D. B. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951, p. 473.

249. Lindsley, D. B. and W. S. Hunter. *Proc. Nat. Acad. Sc., Washington* 25: 180, 1939.
250. Lindsley, D. B. and W. H. Sassaman. *J. Neurophysiol.* 1: 342, 1938.
251. Lindsley, D. B., L. H. Schreiner, W. B. Knowles and H. W. Magoun. *Electroencephalog. & Clin. Neurophysiol.* 2: 483, 1950.
252. Lindsley, O. R. and W. W. Jetter. *Am. Psychologist* 8: 390, 1953.
253. Lowenstein, O. and E. D. Friedman. *A.M.A. Arch. Ophth.* 27: 969, 1942.
254. Luria, A. R. *The Nature of Human Conflicts.* New York: Liveright, 1932.
255. MacLean, P. D. *Psychosom. Med.* 11: 338, 1949.
256. MacLean, P. D. *Electroencephalog. & Clin. Neurophysiol.* 4: 407, 1952.
257. MacLean, P. D. *J. Neurosurg.* 11: 29, 1954.
258. MacLean, P. D. *A.M.A. Arch. Neurol. & Psychiat.* 73: 130, 1955.
259. MacLean, P. D. *Psychosom. Med.* 17: 355, 1955.
260. MacLean, P. D. and J. M. R. Delgado. *Electroencephalog. & Clin. Neurophysiol.* 5: 91, 1953.
261. Mahl, G. F. *Psychosom. Med.* 14: 182, 1952.
262. Mahl, G. F. *Ann. New York Acad. Sc.* 56: 240, 1953.
263. Mahl, G. F. and E. B. Brody. *A.M.A. Arch. Neurol. & Psychiat.* 71: 314, 1954.
264. Mahl, G. F. and R. Karpe. *Psychosom. Med.* 15: 312, 1953.
265. Maier, N. R. F. *Frustration—The Study of Behavior without a Goal.* New York: McGraw-Hill, 1949.
266. Malmo, R. B. *Tr. New York Acad. Sc.* 18: 545, 1956.
267. Mason, J. W. *J. Clin. Endocrinol.* 16: 914, 1956.
268. Mason, J. W. and J. V. Brady. *Science* 124: 983, 1956.
269. Mason, J. W., J. V. Brady and M. Sidman. *Endocrinology* 60: 741, 1957.
270. Masserman, J. H. *A.M.A. Arch. Neurol. & Psychiat.* 39: 1250, 1938.
271. Masserman, J. H. *Psychosom. Med.* 3: 3, 1941.
272. Masserman, J. H. *Am. J. Psychiat.* 98: 633, 1942.
273. Masserman, J. H. *Behavior and Neurosis.* Chicago: Univ. Chicago Press, 1943.
274. Masserman, J. H. In: *Feelings and Emotions*, edited by M. L. Reymert. New York: McGraw-Hill, 1950, p. 40.
275. Masserman, J. and C. Pechtel. *Am. J. Psychiat.* 112: 865, 1956.
276. McDougall, W. *An Introduction to Social Psychology* (2nd ed.). Boston: Tuce, 1926.
277. McTeer, W. *Psychol. Rev.* 60: 172, 1953.
278. Mettler, F. A. *Selective Partial Ablation of the Frontal Cortex.* New York: Hoeber, 1949.
279. Mettler, F. A. (editor). *Psychosurgical Problems.* New York: Blakiston, 1952.
280. Meyer, M. *Psychol. Rev.* 40: 292, 1953.
281. Miller, N. E. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951, p. 435.
282. Milner, P. *Psychol. Bull.* 51: 42, 1954.
283. Mishkin, M. *J. Comp. & Physiol. Psychol.* 47: 187, 1954.
284. Mishkin, M. and K. H. Pribram. *J. Comp. & Physiol. Psychol.* 47: 14, 1954.
285. Mittelmann, B. and H. G. Wolff. *Psychosom. Med.* 1: 271, 1939.
286. Mittelmann, B. and H. G. Wolff. *Psychosom. Med.* 5: 211, 1943.
287. Moniz, E. *Tentatives Operatoires dans le Traitment de Certaines Psychoses.* Paris: Masson, 1936.
288. Morin, G., H. Gastaut, R. Vigouroux, and A. Roger. *Compt. rend. Soc. de biol.* 146: 1959, 1952.
289. Morse, W. H. and R. J. Herrnstein. *Ann. New York Acad. Sc.* 65: 303, 1956.
290. Morse, W. H. and R. J. Herrnstein. *Am. Psychologist* 11: 430, 1956.
291. Moruzzi, G. and H. W. Magoun. *Electroencephalog. & Clin. Neurophysiol.* 1: 455, 1949.
292. Mowrer, O. H. *Learning Theory and Personality Dynamics.* New York: Ronald, 1950.
293. Mulder, D. W. and D. Daly. *J.A.M.A.* 150: 173, 1952.
294. Nauta, W. J. H. *J. Neurophysiol.* 9: 285, 1946.
295. Nauta, W. J. H. *J. Comp. Neurol.* 104: 247, 1956.
296. Nauta, W. J. H. and P. A. Gygax. *Stain Technol.* 29: 92, 1954.
297. Newman, E. B., F. T. Perkins and R. H. Wheeler. *Psychol. Rev.* 37: 305, 1930.
298. Notterman, J. M., W. N. Schoenfeld and P. J. Bersh. *J. Comp. & Physiol. Psychol.* 45: 1, 1952.
299. Olds, J. In: *Nebraska Symposium on Motivation*, edited by M. R. Jones. Lincoln: Univ. Nebraska Press, 1955, p. 73.
300. Olds, J. *J. Comp. & Physiol. Psychol.* 49: 281, 1956.
301. Olds, J. and P. Milner. *J. Comp. & Physiol. Psychol.* 47: 419, 1954.
302. Papez, J. W. *A.M.A. Arch. Neurol. & Psychiat.* 38: 725, 1937.
303. Pechtel, C., J. Masserman, L. Schreiner and M. Levitt. *J. Nerv. & Ment. Dis.* 121: 26, 1955.
304. Penfield, W. and H. Jasper. *Epilepsy and the Functional Anatomy of the Human Brain.* Boston: Little, 1954.
305. Pincus, G. and H. Hoagland. *J. Aviation Med.* 14: 173, 1943.
306. Poirier, L. J. *J. Comp. Neurol.* 96: 209, 1952.
307. Pool, J. S. *J. Neurosurg.* 11: 45, 1954.
308. Porter, R. W. *Am. J. Physiol.* 172: 515, 1953.
309. Pribram, K. H., and M. Bagshaw. *J. Comp. Neurol.* 99: 347, 1953.
310. Pribram, K. H. and J. F. Fulton. *Brain* 77: 34, 1954.
311. Pribram, K. H. and L. Kruger. *Ann. New York Acad. Sc.* 58: 109, 1954.
312. Pribram, K. H., M. Mishkin, H. E. Rosvold and S. J. Kaplan. *J. Comp. & Physiol. Psychol.* 45: 565, 1952.
313. Pribram, K. H. and L. Weiskrantz. *J. Comp. & Physiol. Psychol.* 50: 74, 1957.
314. Ranson, S. W. *A.M.A. Arch. Neurol. & Psychiat.* 41: 1, 1939.
315. Ranson, S. W. and H. W. Magoun. *Ergebn. Physiol.* 41: 56, 1939.
316. Ranstrom, S. *The Hypothalamus and Sleep Regulation.* Uppsala: Almqvist, 1947.
317. Reiser, M. F., R. B Reeves and J. Armington. *Psychosom. Med.* 17: 185, 1955.
318. Reusch, J. and J. E. Finesinger. *A.M.A. Arch. Neurol. & Psychiat.* 50: 439, 1943.
319. Riogh, D. McK. *Psychiatry* 1: 339, 1938.
320. Rose, J. E. and C. N. Woolsey. *J. Comp. Neurol.* 89: 279, 1948.

321. Rosvold, H. E., A. F. Mirsky and K. H. Pribram. *J. Comp. & Physiol. Psychol.* 47: 173, 1954.
322. Rothfield, L. and P. Harmon. *J. Comp. Neurol.* 101: 265, 1955.
323. Rothmann, H. *Ztschr. ges. Neurol. Psychiat.* 87: 247, 1923.
324. Rucknick, C. A. *The Psychology of Feeling and Emotion.* New York: McGraw-Hill, 1936.
325. Sartre, J. P. *The Emotions.* New York: Philos. Libr., 1948.
326. Sawa, M., Y. Ueki, M. Arita and T. Harada. *Folia psychiat. neurol. Japonica* 7: 309, 1954.
327. Sawyer, C. H. *Am. J. Physiol.* 180: 37, 1955.
328. Schaltenbrand, G. and S. Cobb. *Brain* 53: 449, 1930.
329. Schlosberg, H. *Psychol. Rev.* 61: 81, 1954.
330. Schoenfeld, W. N. In: *Anxiety*, edited by P. Hoch and J. Zubin. New York: Grune, 1950, p. 70.
331. Schreiner, L. and A. Kling. Medical Film, U.S. Army 8-7935, 1953.
332. Schreiner, L. and A. Kling. *J. Neurophysiol.* 16: 643, 1953.
333. Schreiner, L. and A. Kling. *A.M.A. Arch. Neurol. & Psychiat.* 72: 180, 1954.
334. Schreiner, L. and A. Kling. *Am. J. Physiol.* 184: 486, 1956.
335. Schreiner, L., D. Rioch, C. Pechtel and J. Masserman. *J. Neurophysiol.* 16: 254, 1953.
336. Segundo, J. P., R. Arana, E. Migliaro, J. Villar, A. Guelfi and E. Austt. *J. Neurophysiol.* 18: 96, 1955.
337. Shapiro, A. P. and P. W. Horn. *J. Nerv. & Ment. Dis.* 122: 222, 1955.
338. Sheer, D. and D. C. Kroeger (editors). *Electrical Stimulation of the Brain. Subcortical Integrative Systems.* Austin: Univ. Texas Press, 1960.
339. Sidman, M. *Science* 118: 157, 1953.
340. Sidman, M. *Science* 122: 925, 1955.
341. Sidman, M. *Ann. New York Acad. Sc.* 65: 282, 1956.
342. Sidman, M., J. V. Brady, J. Boren, D. Conrad and A. Schulman. *Science* 122: 830, 1955.
343. Sidman, M., R. J. Herrnstein and D. Conrad. *J. Comp. & Physiol. Psychol.* 50: 18, 1957.
344. Silverman, J. J. and V. E. Powel. *Am. J. M. Sc.* 208: 297, 1944.
345. Skinner, B. F. *The Behavior of Organisms: An Experimental Analysis.* New York: Appleton, 1938.
346. Skinner, B. F. *Am. Psychologist* 8: 69, 1953.
347. Skinner, B. F. *Science and Human Behavior.* New York: Macmillan, 1953.
348. Skinner, B. F., H. C. Solomon and O. R. Lindsley. *J. Nerv. & Ment. Dis.* 120: 403, 1954.
349. Smith, G. E. *J. Anat.* 30: 185, 1896.
350. Smith, W. K. *Fed. Proc.* 3: 42, 1944.
351. Smith, W. K. *Fed. Proc.* 9: 118, 1950.
352. Solomon, R. L. and E. S. Brush. In: *Nebraska Symposium on Motivation*, edited by M. R. Jones. Lincoln: Univ. Nebraska Press, 1956, p. 142.
353. Solomon, R. L. and L. C. Wynne. *Am. Psychologist* 5: 264, 1950.
354. Solomon, R. L. and L. C. Wynne. *Psychol. Rev.* 61: 353, 1954.
355. Spiegel, E. A., H. R. Miller and M. J. Oppenheimer. *J. Neurophysiol.* 3: 538, 1940.
356. Spiegel, E. A. and H. T. Wycis. *Proc. Roy. Soc. Med.* Suppl. 42: 84, 1949.
357. Spiegel, E. A., H. T. Wycis, H. Freed and C. Archinik. *Am. J. Psychiat.* 108: 426, 1951.
358. Staudt, V. M. and J. F. Kubis. *J. Psychol.* 25: 443, 1948.
359. Stein, L. *Science* 124: 1082, 1956.
360. Stellar, E. *Psychol. Rev.* 1: 61, 1954.
361. Streb, J. M. and K. Smith. *J. Comp. & Physiol. Psychol.* 48: 126, 1955.
362. Taylor, J. (editor). *Selected Writings of John Hughlings Jackson.* London: Hodder & Stoughton, 1932, p. 162.
363. Terzian, H. and G. D. Ore. *Neurology* 5: 373, 1955.
364. Thiesen, J. W. *Arch. Psychol.* No. 285, 1943.
365. Thompson, A. F. and A. E. Walker. *A.M.A. Arch. Neurol. & Psychiat.* 65. 251, 1951.
366. Tilney, F. *The Master of Destiny.* New York: Doubleday, 1930.
367. Todd, T. W. and M. E. Rowlands. *J. Comp. Psychol.* 10: 167, 1930.
368. Tolman, E. C. *Psychol. Rev.* 30: 217, 1923.
369. Ule, G. *Fortschr. Neurol., Psychiat.* 22: 510, 1954.
370. Ulett, G. A. and G. Gleser. School of Aviation Medicine Report, Proj. No. 21-020-0007, No. 4, 1953.
371. Ulett, G. A., G. Gleser, A. Lawler and G. Winokur. School of Aviation Medicine Report, Proj. No. 21-37-002, No. 4, 1952.
372. Ulett, G. A., G. Gleser, P. Starr, J. Haddock, L. Lingley and A. Lawler. School of Aviation Medicine Report, Proj. No. 21-0202-0007, No. 5, 1953.
373. Verhave, T. *J. Pharmacol. & Exper. Therap.* 119: 164, 1957.
374. Verhave, T., J. E. Owen and I. H. Slater. *Progr. Neurobiol., Amst.* 1958.
375. Verney, E. B. *Proc. Roy. Soc., London. ser. B* 135: 24, 1947.
376. Wade, M. *J. Comp. Neurol.* 96: 179, 1952.
377. Walker, A. E., A. F. Thompson and J. D. McQueen. *Bull. Johns Hopkins Hosp.* 93: 65, 1953.
378. Walker, K. C. *J. Exper. Psychol.* 31: 312, 1942.
379. Walter, W. G. *J. Ment. Sc.* 96: 1, 1950.
380. Walter, W. G. *The Living Brain.* New York: Norton, 1953.
381. Ward, A. A., Jr. *J. Neurophysiol.* 11: 13, 1948.
382. Waterhouse, I. K. *J. Comp. & Physiol. Psychol.* 50: 81, 1957.
383. Watson, J. B. *Behavior, An Introduction to Comparative Psychology.* New York: Holt, 1914.
384. Watson, J. B. *Psychology from the Standpoint of a Behaviorist.* Philadelphia: Lippincott, 1919.
385. Weisenburg, T. H. *Brain* 33: 236, 1910.
386. Weiskrantz, L. *J. Comp. & Physiol. Psychol.* 49: 381, 1956.
387. Weiskrantz, L. and K. H. Pribram. *Electroencephalog. & Clin. Neurophysiol.* 6: 708, 1954.
388. Weiskrantz, L. and W. A. Wilson. *Ann. New York Acad. Sc.* 61: 36, 1955.
389. Weiss, B. *Am. J. Psychiat.* 113: 348, 1956.
390. Welch, L. and J. Kubis. *J. Nerv. & Ment. Dis.* 105: 372, 1947.
391. Welch, L. and J. Kubis. *J. Psychol.* 23: 83, 1947.
392. Wenger, M. A. and M. Ellington. *Psychosom. Med.* 5: 241, 1943.

393. Wenger, M. A. and J. C. Gilchrist. *J. Exper. Psychol.* 38: 757, 1948.
394. Wheatley, M. D. *A.M.A. Arch. Neurol. & Psychiat.* 52: 296, 1944.
395. White, J. C. In: *The Hypothalamus and Central Levels of Autonomic Function*, edited by J. Fulton. Baltimore: Williams & Wilkins, 1940, p. 854.
396. Whitehorn J. C., M. R. Kaufman and J. M. Thomas *A.M.A. Arch. Neurol. & Psychiat.* 33: 712, 1935.
397. Williams, A. C., Jr. *Arch. Psychol.* No. 240, 1939.
398. Wilson, M. P. and F. S. Kelier. *J. Comp. & Physiol. Psychol.* 46: 190, 1953.
399. Winsor, A. L. and B. Korchin. *J. Exper. Psychol.* 23: 62, 1938.
400. Winsor, A. L. and B. Korchin. *J. Gen. Psychol.* 22: 25, 1940.
401. Woodworth, R. S. and C. S. Sherrington. *J. Physiol.* 31: 234, 1904.
402. Wundt, W. *Outlines of Psychology* (2nd ed.), translated by C. Judd. Leipzig: Englemann, 1902.
403. Young, P. T. *Emotion in Man and Animal.* New York: Wiley, 1943.
404. Young, P. T. In: *Methods of Psychology*, edited by T. G. Andrews. New York: Wiley, 1948, p. 348.

# Attention, consciousness, sleep and wakefulness

DONALD B. LINDSLEY | *Departments of Psychology and Physiology, University of California, Los Angeles, California*

CHAPTER CONTENTS



THE TERMS attention, consciousness, sleep and wakefulness are a part of our everyday language, and we seem to understand, at least in a general way, what is meant by them. As scientific investigators, however, we are often loathe to attempt a definition of these terms because there are too many unknown or variant conditions involved, or because to limit oneself to a given criterion, or even a set of criteria, may not account for all examples.

We are fully aware from our own experiences, as well as those reported by others, that an attentive set or posture toward a given object in the environment does not always result in awareness and perception of the object. Furthermore, experiments have shown that a pre-established set or intention to respond as quickly as possible to the onset of a specific stimulus does not lead to uniform reaction times; there may be wide variations in response to successive stimuli. Thus, due apparently to spontaneous fluctuations of some process controlling attention, or due to distractions produced by competing stimuli, ideas and thoughts of past experience, one may look directly at an object and not see it, or overlook the cue to respond to a given stimulus with resulting delay or complete absence of response.

The following are a few examples of some of the vagaries of attention in which the behavioral attitude or set may belie the actual attentional and perceptual attitude. The astronomer waiting for the exact instant of a stellar transit across his telescope may miss it due to a lapse of attention or daydreaming. The radar operator waiting for the unusual and unexpected 'blip' on his radar screen may not be ready to report it when it appears among other signals, due to peripheral sensory or central ideational distractions. The sonar operator listening for the special 'ping' of the enemy submarine by sound-echo return may become habituated to the repeated sounds and noises and miss the critical signal.

Thus the temporal course of consciousness or awareness may show many vicissitudes. Often these can be determined and assessed by introspection or subjective report after the fact, but with possible loss of information and sequence because of fallibility resulting from attempting to 'observe' both external and internal events. If we require an immediate verbal

report upon events as they happen, or a reaction to test stimuli periodically inserted while in process of attending to a series of on-going events, we may interfere with that process or destroy its efficacy. If, by preliminary instructions, we attempt to structure an attitude or set to particular events as they occur, we encourage anticipation and watchful waiting which may interfere with, or seriously limit, the process. Naturalness and freedom of response are curtailed, and association between present and past experience may become seriously restricted.

For many years attention and consciousness were considered proper subjects for psychological study by the method of introspection. In the second and third decades of the present century the behavioristic movement in American psychology, fostered by J. B. Watson, E. B. Holt, A. P. Weiss and others, rejected the idea of subjective descriptions of experiences and abandoned the use of the concepts of attention and consciousness. They substituted description and measurement of overt behavioral responses, including vocal, subvocal and other responses of semiovert nature, detectable only by special measuring or recording instruments. From the point of view of objective measurement and the establishment of reliable, though perhaps limited, criteria of response, this was an advance. However, it overlooked the fact that not all stimulation which is capable of excitation of, or influence upon, the central nervous system results in overt behavior of an immediate and measurable nature. Although behavioral criteria of sleep and wakefulness, and even of attention and consciousness, may be established, it has become apparent that one cannot depend solely upon these criteria. In fact the very essence of attention and consciousness now seems to reside in shifting processes and states within the central nervous system, some of which are detectable through changes in

TABLE 1. *Psychological States and Their EEG, Conscious and Behavioral Correlates**

| Behavioral Continuum | Electroencephalogram | State of Awareness | Behavioral Efficiency |
|---|---|---|---|
| Strong, excited emotion; fear, range, anxiety | Desynchronized: low to moderate amplitude; fast mixed frequencies | Restricted awareness; divided attention; diffuse, hazy; 'confusion' | Poor: lack of control, freezing up, disorganized |
| Alert attentiveness | Partially synchronized: mainly fast low-amplitude waves | Selective attention, but may vary or shift; 'concentration' anticipation; 'set' | Good: efficient, selective, quick reactions; organized for serial responses |
| Relaxed wakefulness | Synchronized: optimal alpha rhythm | Attention wanders– not forced; favors free association | Good: routine reactions and creative thought |
| Drowsiness | Reduced alpha and occasional low-amplitude slow waves | Borderline partial awareness; imagery and reverie; 'dream-like' states | Poor: uncoordinated, sporadic, lacking sequential timing |
| Light sleep | Spindle bursts and slow waves (larger); loss of alphas | Markedly reduced consciousness (loss of consciousness); dream state | Absent |
| Deep sleep | Large and very slow waves (synchrony but on slow time bases); random irregular pattern | Complete loss of awareness (no memory for stimulation or for dreams) | Absent |
| Coma | Isoelectric to irregular large slow waves | Complete loss of consciousness; little or no response to stimulation; amnesia | Absent |
| Death | Isoelectric: gradual and permanent disappearance of all electrical activity | Complete loss of awareness as death ensues | Absent |

* From Lindsley (159).

electrical potentials recorded indirectly and diffusely from the brain, or directly and focally in certain regions of the brain.

The electrophysiological changes in the brain, when coupled with behavioral observations and measurements and, in the case of humans, with subjective reports, show remarkable correspondences among these diverse criteria. The electroencephalogram (EEG) has proved to be one of the more reliable and less disrupting methods of studying the transition from wakefulness to sleep, and the reverse. It reveals several distinct stages in the process of going from wakefulness to deep sleep. It permits continuous monitoring of sleep without disturbance to the sleeper, as may be the case with test stimuli applied to determine the threshold for behavioral or subjective response. Insofar as they are applicable, the criteria of depth of sleep revealed by the latter methods correspond well with those of the EEG. Furthermore by combined use of EEG, behavioral and subjective methods, it has become possible to view the differential and gradational stages of attention and consciousness upon the same continuum with those of wakefulness and sleep (see fig. 11 and table 1).

The neural mechanisms which underlie these changes are gradually being revealed, and with this increased understanding have come new concepts of the functional organization of the brain. Awake or asleep, the characteristic rhythms and patterns of electrical activity in the brain appear to regulate not only the discharge patterns of individual neurons and of the aggregates of which they are a part, but of other neurons and aggregates more widely dispersed. Whether such interactions within the brain are accomplished by direct connections, by resonance effects, by field effects or by other means yet unknown remains to be determined. Regardless of how the interactions take place, it is known that certain differential electrical patterns exist at any moment in widely dispersed regions of the brain, and that a certain amount of correlation has already been demonstrated between these electrophysiological patterns and the behavioral and subjective indices of attention, consciousness, wakefulness and sleep.

## NEUROPHYSIOLOGICAL MECHANISMS

During the past 30 years electroencephalographic and neurophysiological studies have provided evidence that attention, consciousness and sleep depend upon a common neurophysiological mechanism. In broad functional outline this mechanism has been described as the ascending reticular activating system (ARAS), with origins in the reticular formation of the lower brain stem and with upward extensions including parts of the hypothalamus, subthalamus and thalamus. (This system is the subject of Chapter LII of this *Handbook*.) Integral with, or closely related to, the ARAS is the diffuse thalamocortical projection system (DTPS), with origins in the nonspecific nuclei of the thalamus (discussed in chapter LIII). These neuroanatomically and functionally related neuronal systems of the lower brain stem and diencephalon provide not only a basis for understanding sleep and wakefulness, but also make possible some meaningful correlations between neurophysiological, behavioral and psychological events which help to define the limits of the various states or gradations of attention and consciousness. The manner in which neuroanatomical, neurophysiological, electroencephalographic, behavioral and psychological data conjoin to support the above statements will be presented in subsequent sections of this chapter.

It is difficult to trace the origin of the ideas which have led to a new concept or theory, or to decide at what critical juncture the accumulated experimental evidence established confirmation of the theory. However, with respect to the functional concept of the ARAS and the role it plays in sleep and wakefulness, as well as in electrocortical activation and behavioral alerting, there is little doubt that Moruzzi & Magoun (181), and subsequently Magoun and his collaborators (78 80, 163, 164, 172), clearly and firmly laid the groundwork for an important new concept of brain organization in relation to behavior.

Similarly, following upon the pioneering work of Morison & Dempsey (59, 60, 179, 180) in which they described the very significant 'recruiting' and 'augmenting' responses elicited in the cortex by stimulation of certain regions of the thalamus, Jasper and collaborators (95, 96, 126, 130–132) in a series of experiments have outlined some of the functional relationships of the diffuse thalamocortical projection system (DTPS). Jasper (127, 128) has further proposed some important functions which this system, in conjunction with the ARAS, may play in relation to consciousness and attention. Tissot & Monnier (225) and Monnier *et al.* (176) have recently provided additional information of importance to the understanding of the roles of the ARAS and DTPS.

The pictures of both the ARAS and the DTPS have been painted in broad and bold strokes, but the outlines of the figures are unmistakable. These concepts

have stimulated much new investigation and work goes on apace all over the world. There remains much fine detail to fill in, and corrections and additions have already been made. There is a need to develop further extensions and modifications of these views so as to encompass more of the higher functions of which man and his near relatives in the animal kingdome are capable. Perception, memory, learning, emotion and motivation are some of the psychological problems currently being pursued intensively by further investigation of the ARAS and the DTPS, but especially in ancillary and related systems elsewhere in the brain stem, limbic system and neocortex.

Let us attempt to trace some of the earlier and alternative views of sleep and wakefulness, and particularly provide some of the background which leads to the present concepts of the ARAS and DTPS. For some reason, perhaps because adult man spends only about one third of his time in sleep, wakefulness has been traditionally thought of as the natural condition and sleep a deviant, but necessary, recuperative period requiring explanation. Hence the persistent search for a sleep or sleep-regulating center in the brain, a sort of magic push button to turn on and off this process. Other conceptions of sleep have emphasized a generalized depression or inhibition of central nervous system function.

Whether a generalized or a local sleep-regulating center was envisaged, the factors responsible for depression or reduction of function in sleep have variously been noted as anemia, accumulation of fatigue products and toxins, periodic change in humoral and endocrine action, change in amount and rate of cerebral circulation, development of a generalized or irradiated internal inhibition, and retraction of dendrites at synaptic junctions. These and other theories have been reviewed by Pieron (195), Ebbecke (68), von Economo (230), Gillespie (91), Kleitman (145), Kayser (140) and Ploog (196).

Concise, but relatively comprehensive, overviews of some of the characteristics of sleep and theories of sleep have been presented by Wiggers (233) and Morgan & Stellar (178). Kleitman's (145) book, *Sleep and Wakefulness*, is a classic in the field.

### *Early Neurophysiological Concepts of Sleep and Wakefulness*

Several viewpoints have held that there is a blockage of afferent impulses at some point in the brain which prevents it from being maintained in an active and wakeful state. These have been called stimulus deficiency theories, and some of them resemble in general notion the modern neurophysiological theory based on the ARAS, but do not, of course, distinguish between the specific and unspecific sensory systems and their respective roles.

Following an epidemic of encephalitis lethargica, with sleep as a prominent sign, Mauthner (175) in 1890 reported clinical and neuropathological evidence of swelling and other lesions in the periventricular and periaqueductal grey matter of the midbrain. The sleep was attributed to a compression of afferent pathways, cutting off the influx of sensory impulses to the brain. Mauthner generalized upon this conclusion based on patients with encephalitis and proposed a midbrain sleep-regulating center which in some manner regulated the flow of impulses to the brain and accounted for sleep in normal persons. von Economo (229), after similar experiences with encephalitis patients following World War I, extended the concepts of Mauthner. Instead of a specific center, he proposed that there is an area reaching from the midbrain through the hypothalamus to the basal ganglia which is concerned with the regulation of sleep and wakefulness. In general the location and structures involved correspond fairly well with the modern neuroanatomical description of the ARAS provided in the extensive review of the reticular formation by Rossi & Zanchetti (204). However, von Economo had rather different ideas about its function. He conceived of two centers of control, one rostrally located in the basal ganglai which was thought to be able to inhibit the activity of the thalamus and cortex and produce disturbances in consciousness and what he called 'brain sleep.' The other he located in the midbrain. It was thought to be inhibitory to vegetative and somatic centers in the posterior hypothalamus and lower brain stem, thus giving rise to 'body sleep.' Numerous facts of normal and pathological sleep fit such a concept, as do some modern concepts of disturbances of consciousness in epilepsy. However, the theory, like so many others, does not make explicit how inhibition or excitation of the centers is effected, nor in what manner these influence central or perpheral functions in sleep and wakefulness.

Many other proposals have been made concerning the so-called sleep and wakefulness centers. For the most part the location was in the posterior hypothalamus, midbrain or thalamus, and overlapped in some degree with the ARAS and DTPS systems described above. The details of the individual viewpoints have been covered in Kleitman's (145) comprehensive survey. Notable, because of one element of similarity to modern views, namely cortical activation of the ARAS, is Kovacs' (149) conception that

sleep is due to anabolic depression of sympathetic activity on the one hand and to reduction of psychic activation on the other. The modern neurophysiological conception recognizes both a peripheral sensory and a central influence upon the activation of the ARAS. Several other views emphasize that in the physiological accompaniments of sleep there is a predominance of parasympathetic influence, in contrast to sympathetic dominance during wakefulness. Marinesco *et al.* (174) believe on the other hand that parasympathicotonia is a cause and not a result of sleep, and that endocrine secretions act as sensitizers of vegetative centers. Their view holds that sleep is a conditioned process and that the circumstances favoring sleep (reduction of stimulation) constitute a conditioning situation which gives rise to the unconditioned humoral and vegetative responses.

Trömner (227) and Spiegel (219) have advocated a sleep-regulating center in the thalamus. Spiegel proposed a primitive center of consciousness in the thalamus, and believes that inhibitory and excitatory interaction between thalamus and cortex may influence consciousness as well as sleep and wakefulness.

Pavlov (189, 190) has described a variety of conditions under which local, and subsequently generalized, inhibition of the cortex develops and leads to sleep. Among these are conditions of extinction of a conditioned response in which the conditioned stimulus is repeatedly presented without adequate reinforcement, or in which delayed reinforcement is unduly prolonged. Some of these conditions of stimulation are reminiscent of the modern concept of 'habituation' described by Hernández-Peón and collaborators (105, 106) but in which the explanation of the effects of repeated stimulation seems to reside in the brainstem reticular formation rather than the cortex as Pavlov maintained. There remains much to be learned about the conditioning phenomena described by Pavlov and the 'habituation' effects studied by Hernández-Peón and others, particularly in terms of their neurophysiological basis.

Hess (111, 112) has described the experimental production of sleep in cats by electrical stimulation in the posterior hypothalamus and along the walls of the third ventricle. These effects were produced by d.c. stimulation which may have produced polarization effects capable of blocking transmission in an area now known to be part of the ARAS and important to the maintenance of arousal and wakefulness. Ranson *et al.* (199), stimulating with faradic current in the same regions of the hypothalamus, were not able to produce sleep. On the contrary, as would now be expected, they produced activity and excitement, apparently due to excitation of portions of the ARAS traversing the posterior hypothalamic region.

The more recent work of W. R. Hess (113–117) and of his son, R. Hess, and collaborators (109, 110) has been summarized in *Brain Mechanisms and Consciousness* (118). They now distinguish two systems represented in different areas or fields which give quite different results upon electrical stimulation. The ergotrophic or 'dynamogenic' field is located in the posterior and mesial part of the hypothalamus, and extends into the mesencephalon. Stimulation in this region, which overlaps with the ARAS, is said to produce excitement and arousal which Hess describes as mobilization and preparation for defense. Others from the time of Karplus & Kreidl (139) have, of course, found this general region favorable to the production of sympathetic nervous system effects associated with arousal and mobilization (18, 138, 200). In contrast to this field of general excitability and alertness, Hess describes another which he calls the trophotropic field or 'hypnogenic' center. This region of the diencephalon lies lateral to the massa intermedia, and extends caudally to the habenulopeduncular tract and rostrally to the mammillothalamic bundle. Medially it is 1.5 to 2 mm from the mid-line. Its lateral boundaries have not been determined due to technical difficulties. Stimulation of this trophotropic region with slowly rising d.c. pulses of 1 to 2 v. and a frequcy of 4 to 12 per sec. causes a generalized depression of activity and sleep, capable of reversal by stronger or higher frequeney shocks. The electrocortical activity and behavior induced by low-frequency stimulation in this zone is said to be indistinguishable from natural sleep. As its name implies, its significance is believed to be the preservation of energetic resources, and the reparation and protection of tissues from overstrain. It is thought to function as an antagonist to the arousal system.

The trophotropic system of Hess overlaps with the region in which Morison & Dempsey (59, 179) and others (222, 223) have consistently produced 'recruiting responses' in the cortex at similar frequencies of stimulation, but from which higher frequency of stimulation (50 to 300 per sec.) produces instead cortical desynchrony or activation and behavioral arousal. The fact that both the ergotropic and trophotropic systems overlap to some extent with the ARAS, and also the DTPS, would easily account for the activation and arousal responses with high-frequeney stimulation. The results of low-frequeney stimulation in the trophotropic area are less easily accounted for. They undoubtedly produce recruiting responses similar to those of Morison & Dempsey with corre-

sponding synchronized cortical waves of high voltage, perhaps favoring sleep. It would also seem possible that the slowly rising d.c. pulses might block the influences of the ARAS in maintaining wakefulness, by electrotonic or polarization effects. It has been argued by Hess that this is not the case since the same type of stimulus has been applied in the ergotropic center with excitatory rather than depressive and sleeplike results.

Nauta's (182) results on sleep in the rat in some respects agree with those of Hess and in other respects are more closely related to the work of Ranson's group. He believes there is a center for sleep in the preoptic and suprachiasmatic regions, and that there exists in the mammillary region a center for wakefulness. According to Nauta the center for wakefulness plays a predominant role, and the sleep center of the anterior hypothalamus serves mainly a modulatory function upon the activity of the center of wakefulness.

### *Origins of the Ascending Reticular Activating System Concept*

Our present knowledge of the ascending reticular activating system (ARAS) derives from the discovery by Moruzzi & Magoun (181) that stimulation of the reticular formation of the lower brain stem in the cat produces electrocortical 'activation' or 'desynchronization' and behavioral arousal. This recognition of the ARAS as a second or unspecific sensory system which plays a very significant role not only in the regulation of sleep and wakefulness, but as a potential integrator of other important functions mediated by the central nervous system has led to some entirely new concepts of brain function.

Such an important discovery could scarcely have been made had it not been for certain antecedent experiments and observations by others. Among these were the pioneering experiments of Berger (19–22) who first successfully described the human electroencephalogram in 1929. His general findings were confirmed by Adrian & Matthews (6), and subsequently by a host of others. (See Chapter XI of this *Handbook*.) His work demonstrated that the brain has intrinsic rhythms of its own, among them an 8 to 12 per sec. alpha rhythm which may be blocked by attention and sensory stimulation. He showed that waking and sleeping may be distinguished in the EEG by their different patterns. He also demonstrated that conditions which impair consciousness, such as anesthesia and epileptic states, produce distinctive EEG changes. Each of these early observations was important in its own right, but the fundamental discovery that the brain has an electrical beat, apart from induced activity, was to prove a tremendous stimulus to future work in neurophysiology. Furthermore, the recognition of electrocortical activity and its use as an indicator of cortical activation or arousal was exceedingly important in the subsequent experiments of Bremer (33–35) and Moruzzi & Magoun (181).

As described in the preceding section, the early concepts of sleep and waking centers were gradually being revised in the light of the results of stimulation or of lesions made in the diencephalon and brain stem. In this regard the work of Hess (111, 113, 116) on autonomic centers and the production of sleep by diencephalic stimulation was significant. Perhaps most important of all, since Magoun had been a student of Ranson's and Moruzzi had worked in Bremer's laboratory, were the antecedent experiments by these senior investigators. In an excellent review of the experimental work on the hypothalamus published in 1939, Ranson & Magoun (200) literally anticipated the ARAS concept of a 'waking center.' They stated: "In the hypothalamus and particularly in the posterior part of the lateral hypothalamus is located a mechanism, which when activated excites the entire organism. Here we have the 'waking center'. . . . Furthermore, it has been shown that electrical stimulation of the lateral part of the hypothalamus causes a similar generalized somatic and visceral activation, and, when applied in an unanesthetized cat which has been lying quietly on its side with eyes closed, causes it to become alert, wide awake and intensely excited."

After commenting that the foregoing reaction was due to descending influences, they pointed out: "It is probable that the active hypothalamus not only discharges downward through the brain stem, spinal cord and peripheral nervous system into the body but also upward into the thalamus and cerebral cortex." These remarks indicate that there was a growing awareness of the importance of the caudal portion of the hypothalamus (and elsewhere, the rostral mesencephalon) not only as a 'waking center,' but one capable of arousing and alerting the entire organism.

Bremer (33–35) was the first to demonstrate by electrocortical and behavioral methods that a midbrain transection in the cat, his now famous *cerveau isolé* preparation, produced characteristic signs of profound somnolence. He attributed the sleep thus produced to a generalized deafferentation which at the time, prior to knowledge of the role of the ARAS,

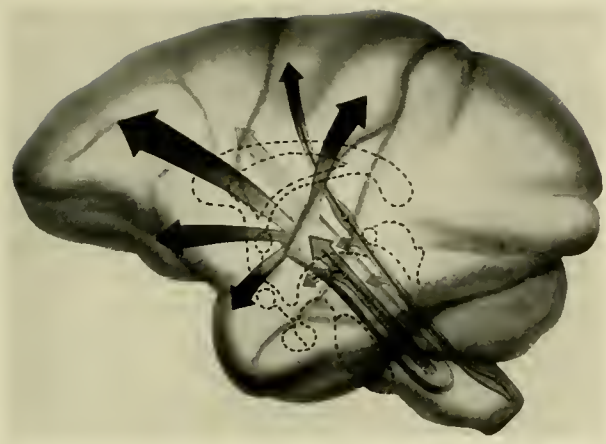


FIG. 1. Ascending reticular activating system (ARAS) schematically projected on monkey brain. The reticular formation, consisting of the multineuronal, multisynaptic central core of the region from medulla to hypothalamus, receives collaterals from specific or classical sensory pathways and projects diffusely upon the cortex. Impulses via specific sensory pathways are brief, discrete, direct and of short latency in contrast to those via the unspecific ARAS which are persistent, diffuse and of long latency.

seemed to imply primarily the elimination of transmission in the classical sensory pathways. Later it was shown by Lindsley *et al.* (163, 164), in both acute and chronic preparations, that the lemniscal pathways would not suffice to maintain the brain and behavior in a waking state when the midbrain tegmentum was transected. Under the reverse condition, with the lemniscal pathways severed and the reticular formation intact, the EEG and behavior were like those in a normal waking animal (see fig. 4). This was subsequently confirmed in the monkey by French & Magoun (78).

One further development should be cited. Although Haenel (93) and Taussig (224) were the first to propose that sleep is essentially a passive state and that wakefulness and consciousness depend upon afferent impulses, Kleitman & Camille (145, 146) were the first to develop, on the basis of experimental evidence, the notion that the waking state depends upon afferent impulses. Kleitman (145) proposed what he refers to as an evolutionary theory of wakefulness which corresponds closely to the neurophysiological results upon which the concept of the ARAS is based. Kleitman held that wakefulness is an active process supported by afferent influx from visceral and somatic sources which keeps the brain awake. This he called 'wakefulness of necessity.' Developing tensions through the course of a night's sleep, as well as intrusions of daytime stimuli, would inevitably awaken the sleeper through impulses imposed upon a waking center which Kleitman presumed to be in the hypothalamus. His second concept was that there is also a 'wakefulness of choice.' This concept left room for habit, learning, conditioning, thought and the like to influence from higher centers the waking center in the diencephalon. Such an arrangement seems now to be entirely possible, since the ARAS has been shown to be activated not only by sensory influx but by corticifugal connections to the reticular formation.

Thus we see that several developments combined to set the stage for the crucial experiment of Moruzzi & Magoun (181). Knowledge of the EEG provided by Berger (19) and the utilization of it by Bremer (33) in connection with his *cerveau isolé* preparation suggested important implications for the lower brain stem with respect to sleep and wakefulness. The extensive search throughout the diencephalon and brain stem by Ranson, Hess and others for autonomic and sleep and wakefulness centers was beginning to focus attention upon new mechanisms. The insightful observations of Ranson & Magoun (200) concerning the descending and ascending influences resulting from stimulation in the brain stem and hypothalamus were also contributory to new ideas. Finally, Magoun and collaborators (165, 173, 209, 221) had studied the descending effects of stimulation and lesions in the brain-stem reticular formation upon spinal reflexes and motor behavior, and had been able to demonstrate a rostral excitatory area and a caudal inhibitory region. With the importance of the reticular formation demonstrated for downstream effects upon spinal reflexes and muscular contractions, there remained the exploration of possible ascending influences suggested by Ranson & Magoun (200). It was precisely these that Moruzzi & Magoun were able to demonstrate.

Figure 1 illustrates schematically the ascending reticular activating system (ARAS) projected upon the monkey brain. Shown here is the pathway of a somesthetic afferent, relaying in the thalamus and proceeding to its destination in the sensory cortex. This represents the specific, primary or classical sensory system. The unspecific or secondary sensory system is represented by the ARAS with origins in the reticular formation of the lower brain stem. This is shown by the darker arrow in the central core of the brain stem with multisynaptic relays schematized. The upward extensions of the ARAS in a diffuse

manner are illustrated by the arrows directed to all parts of the cerebral cortex.

Beginning in the medulla, the reticular formation extends upward through the central core of the brain stem, through the region of the pons, midbrain, hypothalamus, subthalamus and thalamus. Some of its ascending pathways appear to reach the cortex and other forward structures via the internal capsule; others go to the thalamus, especially to the reticular, intrathalamic and other unspecific nuclei. The extrathalamic route appears to provide the ARAS with direct access to widespread cortical areas, whereas the thalamic route brings the ARAS into relation with the DTPS and possibly with the specific relay nuclei as well. Thus the more direct pathways from the reticular formation to the cortex via the internal capsule constitute a possible mechanism subserving preliminary arousal and general alerting of the cortex to impending messages in specific sensory systems. The thalamic component of the ARAS, in conjunction with the DTPS, may provide a kind of scanning and screening mechanism capable of modifying or regulating the influx of messages to the cortex via the specific thalamic relay systems. It may also aid in controlling the distribution and integration of the messages upon arrival at the cortex. As such it may constitute a specific alerting mechanism capable of sharpening and shifting the focus of attention upon a given sense modality or within a modality. Such possibilities will be further discussed in the next section which deals with the DTPS.

To return to the means of excitation of the ARAS, note in figure 1 that the arrows branching off from the classical sensory pathways symbolize collaterals to the reticular formation. Evidence now indicates that every sense modality, apart from its specific or primary message-carrying function, also has connections with some part of the reticular formation and is capable of exciting this structure, thus giving rise to an unspecific or secondary sensory influence as manifested in the activity of the ARAS. Moruzzi & Magoun (181) demonstrated not only that electrical stimulation of the midbrain reticular formation was capable of arousing behaviorally and electrocortically a drowsy, sleeping or lightly anesthetized cat, but that natural sensory stimuli of all types would produce a similar effect. Furthermore in the waking cat the same stimuli led to cortical activation and behavioral alerting. Electrical recording directly from the reticular formation has demonstrated that natural sensory stimuli of all types evoke potentials there. These functional demonstrations of the influence of collaterals from sensory pathways to the reticular formation are in accord with previous neuroanatomical knowledge which has recently been further elaborated by Olszewski (187), Brodal (40), Rossi & Brodal (203) and the Scheibels (206).

Still another mode of excitation of the reticular formation has been demonstrated which is of particular importance to the topics under consideration here. Several investigators (2, 3, 38, 104, 120, 185) have shown that stimulation of various parts of the cortex gives rise to potentials in the brain-stem reticular formation, but in particular the work of French *et al.* (77) may be referred to here. Figure 2 shows schematically both the corticifugal pathways and the collaterals of classical afferent pathways converging upon the reticular formation of the lower brain stem. These of course are by no means the sole afferents to this structure, for others arise in the cerebellum, basal ganglia, thalamus, hypothalamus and rhinencephalon. For an excellent review of the anatomy and physiology of the reticular formation and its afferent and efferent connections, an extensive article by Rossi & Zanchetti (204) should be consulted. Other valuable surveys of the reticular formation are those by Segundo (211), O'Leary & Coben (186) and French in Chapter LII of this *Handbook*.

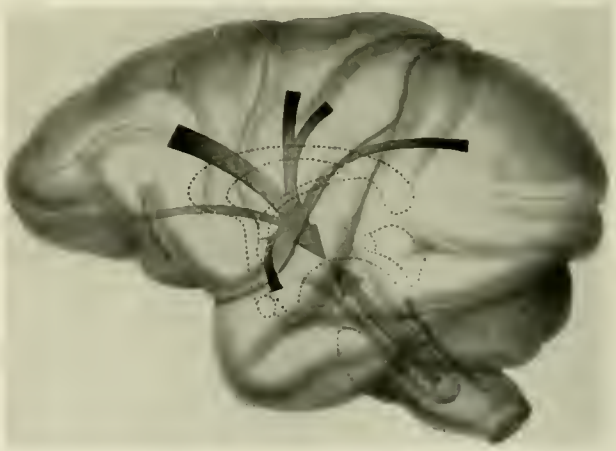


FIG. 2. Corticifugal pathways and collaterals of classical afferent pathways converging on the reticular formation of the lower brain stem. Stimulation of widespread cortical areas gives rise to electric potentials in the reticular formation, hence functional connection by assumed corticoreticular paths. Afferent impulses from all sources and impulses originating in the cortex are capable of exciting the ARAS, which in turn maintains the cortex and behavior in a state of arousal and alertness, and perhaps selectively controls attention. [From French *et al.* (77).]

HYPOTHALAMIC-CORTICAL DISCHARGE CONCEPT. The point of view of Gellhorn (87) concerning the importance of the hypothalamus in relation to sleep and wakefulness, consciousness and attention should also be considered. He has argued on the basis of a variety of experiments that "direct and reflex excitation of the posterior hypothalamus is associated with a diffuse excitation of the cerebral cortex. The intensity of this hypothalamic-cortical discharge is directly related to the excitability of the posterior hypothalamus." He states further: "The hypothalamic-cortical discharge is associated with the state of wakefulness. Conditions which interfere with this discharge cause somnolence and coma." Finally Gellhorn places emphasis upon the role of proprioceptive and nociceptive influences, hypothalamic imbalance, and corticofugal discharges in the maintenance of hypothalamic excitability. The excitability and activation of the hypothalamic-cortical system, maintained from external and internal sources, he believes to be responsible for the maintenance of wakefulness, consciousness and the state of awareness exhibited by perceptual discriminations.

It will be recognized that Gellhorn places his main emphasis upon the hypothalamus and particularly the posterior hypothalamus for the regulation and control of states which many have attributed to the diffuse reticular system, including the ARAS and DTPS. There is no real inconsistency here, however, since the reticular substance extends into the posterior hypothalamus and the upward efferent projections from it extend to and beyond the hypothalamus (204). It seems likely that many of the results reported by Gellhorn and his collaborators might well be accounted for in terms of the ARAS, inclusive of parts of the hypothalamus. However, the importance of many of the autonomic factors considered by Gellhorn should not be overlooked either from the point of their direct influences upon the cortex or their indirect homeostatic influences.

### *Origins and Characteristics of the Diffuse Thalamic Projection System*

Before beginning this topic it may be well to clarify the terminology to be used. Because of the great complexity of interrelationships among diencephalic structures, and particularly those of the thalamus, it will be necessary to deal with a simplified concept of this organization. Thus, following the terminology used by Jasper (130), we will speak of specific and diffuse thalamic projection systems. The topically organized projections from classical sensory relay nuclei upon somewhat delimited cortical receiving areas will be called specific thalamic projection systems (SPTS), while those shown to have a widespread effect upon electrocortical activity, either in terms of activation or recruiting responses, will be referred to as diffuse thalamic projection systems (DTPS). This distinction might be made on the basis of neuroanatomical considerations as well as neurophysiological, but with many more qualifications and much less simplicity. The dorsally placed association nuclei will be included under the diffuse system, although like the specific nuclei they tend to be more topically organized and delimited in their cortical influence.

To use the label 'diffuse thalamic projection system' rather than 'diffuse thalamocortical projection system' takes cognizance of the fact, as pointed out by Droogleever-Fortuyn (65) and Nauta & Whitlock (183), that there is uncertainty that more than a few of the nuclei lumped under the terms diffuse or nonspecific actually project directly to the neocortex. Instead, there is indication that many of them project either to the caudate, striatum or rhinencephalon, or form connections with the dorsal association nuclei, nucleus ventralis anterior and the rostral pole of the reticular nucleus. Among the so-called diffusely projecting nuclei, the reticular complex, according to Rose (201), shows degenerative changes following neocortical ablations, but the temporal character of these is such as to suggest that they may be secondary to degeneration in the dorsal thalamic nuclei. Thus the over-all picture in the thalamus is complex neuroanatomically, and neurophysiologically it is not as easy to categorize the effects produced in the cortex by stimulation as first supposed since there appears to be considerable overlapping and interaction of specific and nonspecific systems. Further details of the relationships of the DTPS or 'unspecific thalamocortical projection system' are taken up by Jasper in Chapter LIII in this *Handbook*.

Ramón y Cajal (198) described two-way connections between thalamus and cortex, and saw in this arrangement a possible means of control by the cortex over the sensory influx via the thalamus, thus affording a possible mechanism of attention. Head & Holmes (97), on the basis of clinical neuropathological data, postulated an inhibitory control of the cortex upon the thalamus which was believed to regulate attention and affect. It was some time later, however, before the method of strychnine neuronography, as developed by Dusser de Barenne & McCulloch (67)

and used also by others (185), was able to demonstrate functional connections between the cortex and specific and nonspecific nuclei.

As early as 1933 Bartley and Bishop (16, 25) were suggesting reverberating circuits between the thalamus and cortex to account for synchronization they observed between alpha-like rhythms of the cortex and activity in the pathways and thalamic nuclei of the visual system. Subsequently Jarcho (124) and Chang (44) also postulated reverberating or loop circuits to account for interactions they observed between the thalamus and cortex. Jarcho believed that the reverberating circuit responsible for repetitive after-potentials was a part of the specific projection system, whereas Chang felt that there were two independent systems, but capable of influencing one another. Chang demonstrated that the second of two click stimuli was able to abolish the recurrent after-potentials which followed the specific evoked response to the first click in the auditory cortex, and that it reset or established its own rhythmic aftereffects. Only when the interval between the two clicks was properly adjusted to the duration of the rhythmic after-potentials of the first evoked response would it give an optimal response. Thus the responses of the specific system are influenced by the recurrent rhythms of the nonspecific system, and the rhythms of the latter system can be influenced or reset by the activity in the specific projection system. This may be an important step in the process of attention and consciousness, and will be discussed in a later section.

Another important neurophysiological clue to the control of attention and consciousness derives from the work of Morison & Dempsey (59, 179) who discovered that stimulation of the mid-line, intralaminar and dorsomedial nuclei of the diffuse thalamic projection system at frequencies of 6 to 12 per sec. in the cat gives rise to a 'recruiting response' in several widespread areas of the cortex. The first three or four shocks to the thalamus produce a gradually increasing magnitude of response in the cortex, hence the term 'recruiting,' implying that more and more units or increments to the field of activity have been brought into synchrony. By about the fifth stimulus the amplitude of the response stabilizes. If a much higher frequency of stimulation is applied to the same electrodes, the recruiting response is abolished and a condition of 'activation' prevails, much like that from stimulation of the reticular formation of the lower brain stem which brings the ARAS into play.

It is interesting that stimulation of the mesencephalic reticular formation with shocks of 100 to 300 per sec. produces electrocortical activation, behavioral arousal and alerting of enduring persistence, whereas similar high-frequency stimulation of the recruiting areas of the thalamus produces the same effects but without long-lasting persistence and with distinctly more limited topographic representation. This again may reflect the relatively different roles of the ARAS and DTPS in the matter of the temporal control and flexibility with respect to attention, the former perhaps determining longer-lasting general states of alertness and the latter modulating these states on a shorter and more variable temporal scale. Other differences in the two systems are reflected in the fact that the recruiting mechanism is not affected by barbiturate anesthesia, either in its low-frequency recruiting response or in its higher frequency activation response, whereas the activation mechanism of the ARAS is seriously disrupted. Still another difference is the tendency, reported by Hess (118) and Akimoto *et al.* (8), for low-frequency stimulation in certain regions of the DTPS to produce sleep, whereas similar stimulation in the reticular formation of the ARAS does not. Such neurophysiological differences serve to distinguish the ARAS and DTPS as having different functional roles, although there is also reason to believe that they may work integratively and in some instances may have mutually reinforcing effects.

One very important point seems to be that the ARAS, except when it is blocked by anesthesia, has an activation effect which takes precedence over that of the DTPS. This would seem to have teleological significance. From a protective viewpoint it would appear to be more important for a general alerting mechanism such as the ARAS to clear the way for any or all warning messages from a threatening environment, than to have the central mechanism, represented by the thalamus and cortex, remain preoccupied with a specific focus of attention and oblivious to danger.

Further distinctions between the ARAS and DTPS are seen in their reactions to drugs and anesthetics. Bonvallet *et al.* (29) by some ingenious experiments demonstrated that epinephrine acts principally on the upper part of the brain-stem reticular formation to produce activation of the ARAS, with accompanying electrocortical activation or arousal. This effect was shown by these authors, and by Rothballer (205), to be limited to the pontomesencephalic reticular formation, since lesion of the ARAS at the junction of the midbrain and diencephalon prevented epinephrine from having this effect. Thus the upper midbrain

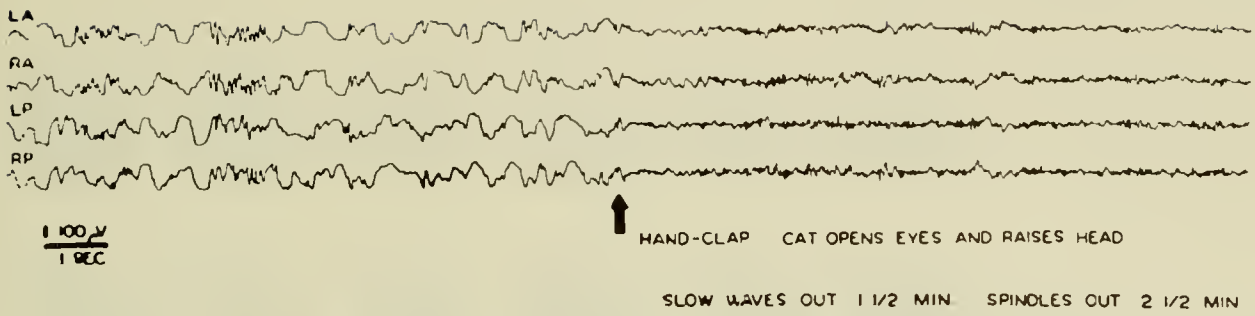



FIG. 3. Arousal of a sleeping cat by auditory stimulus and shift of electrocortical activity from slow waves and spindle bursts of sleep to low-voltage fast activity called activation. Left and right, anterior and posterior recordings all show same diffuse effect of activation. [From Lindsley *et al.* (164).]

portion of the ARAS is epinephrine-sensitive and gives rise to persisting tonic activation influences, whereas the DTPS does not. Although the evidence is not perfectly clear, due to conflicting results by different workers, there are nevertheless indications that activation or behavioral arousal responses, or both, elicited from ARAS and DTPS are somewhat differentially affected by mephenesin, chlorpromazine and barbiturates (30, 32, 70, 143).

### *ARAS and DTPS Arousal and Alerting Effects*

Lindsley *et al.* (164) have shown the nature of electrocortical 'arousal' and its association with behavioral arousal in the cat (see fig. 3). It will be noted that the sleeping cat's EEG record shows irregular slow waves and periodically occurring spindle bursts composed of 12 to 14 per sec. waves. An auditory stimulus, such as a sharp hand-clap, caused the EEG picture to change immediately to a low-amplitude fast-activity pattern, without slow waves or spindle bursts. Associated with this was behavioral arousal consisting of opening of the eyes and raising of the head. The EEG sleep picture was not restored for at least 2 or 3 min. when the cat again assumed a sleeping posture. Thus the association between electrocortical 'arousal' and behavioral arousal was established, and although exceptions to this have been reported under the influence of certain drugs (31, 82, 234), especially atropine, repeated confirmation has permitted the general use of electrocortical and behavioral arousal interchangeably.

Figure 4 illustrates how intactness of the reticular formation is essential to wakefulness and how its interruption produces somnolence or sleep. Section confined to the lateral afferent pathways in the midbrain region of the cat still permits behavioral (*A*) and

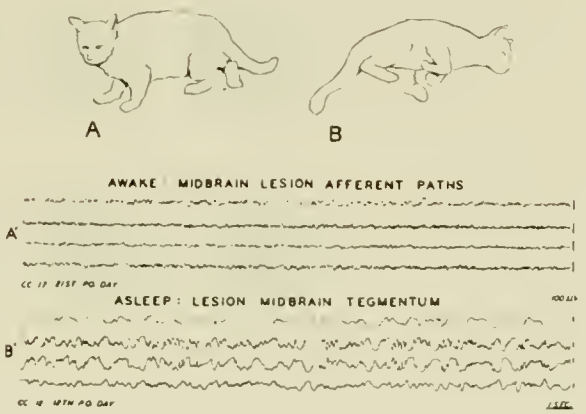



FIG. 4. Cat with bilateral section of the classical afferent pathways in the midbrain, sparing the tegmentum, standing awake (*A*), with characteristic waking EEG (*A'*). Cat with mesencephalic tegmentum interrupted, sparing the classical afferent pathways, lies somnolent (*B*), with sleeping EEG (*B'*). [From Lindsley *et al.* (164).]

electrocortical (*A'*) wakefulness. Note that the electrocortical activity is characteristic of waking in a normal cat, with low-amplitude fast activity predominating, and that behaviorally the cat is awake. In contrast to this, after a lesion of the midbrain tegmentum, interrupting the ARAS, the behavior (*B*) and the electrocortical activity (*B'*) are those of somnolence or sleep. In such a state the animal can be aroused only momentarily by strong stimuli, and the electrocortical and behavioral arousal do not persist after the stimulation has ceased.

Segundo and co-workers (212) have demonstrated in the monkey how arousal and alerting may be produced by reticular stimulation. Figure 5 illustrates how an otherwise normal monkey, with electrodes chronically implanted in the reticular formation and also over the temporal and frontal poles of the cortex,

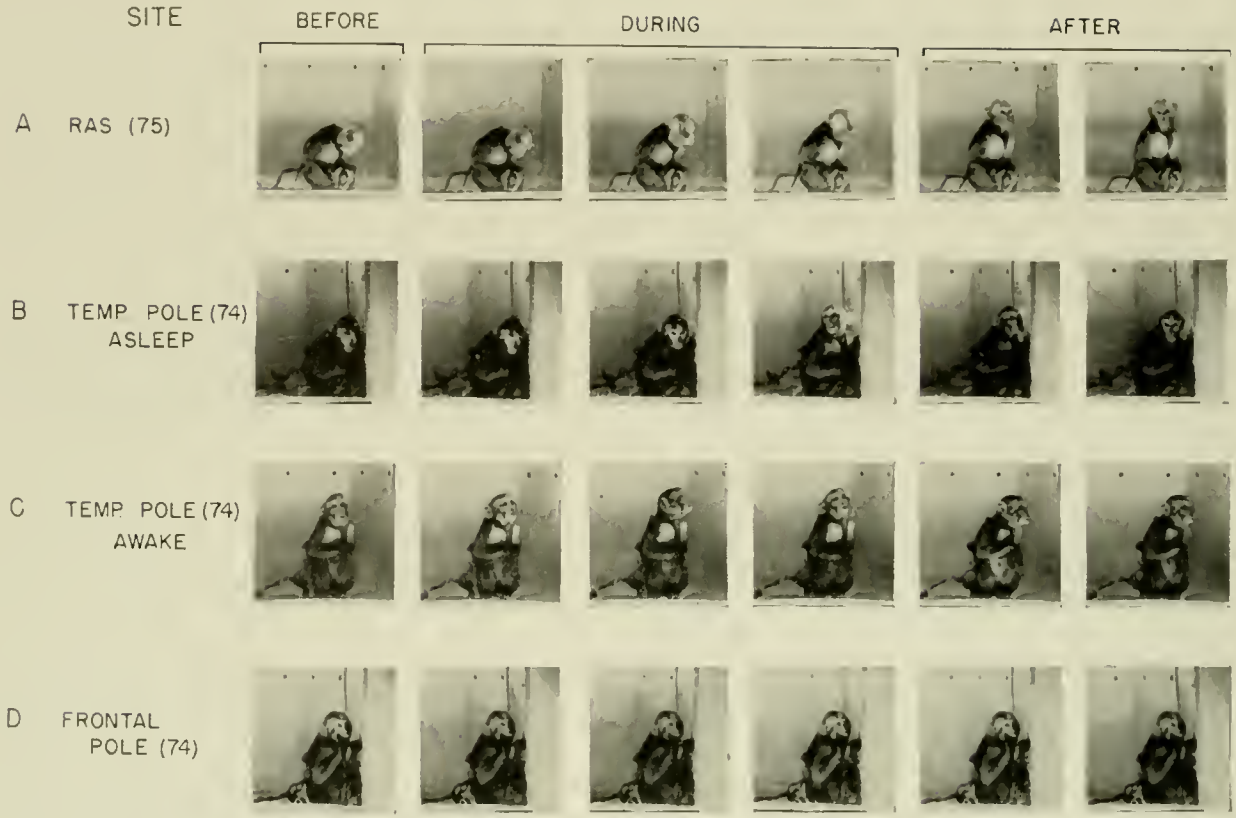



FIG. 5. Behavioral arousal of a sleeping monkey by electrical stimulation through implanted electrodes in the reticular formation (*A*) and on the temporal pole of the cortex (*B*). Stimulation of the temporal pole of a waking monkey alerts it to attention (*C*), but stimulation of the frontal pole is ineffective (*D*).

reacts to stimulation in each of these regions. In picture-series *A*, while the monkey is asleep, the reticular formation (RAS) was stimulated. Note progressive arousal from a sleep posture before stimulation to an alert and upright posture with an inquiring appearance after the stimulation ceased. The same behavior occurred (*B*) when the temporal pole was stimulated during sleep. Stimulation of the temporal pole while the monkey was awake (*C*) caused the monkey to look more alert and to scan the environment for the source of the alerting stimulus, finally fixing attention in a given direction. Stimulation of the frontal pole (*D*), an area less able apparently to activate the ARAS or to mobilize attention through the DTPS, although receiving projections from certain portions of the DTPS, results in no apparent change in behavior.

It has been pointed out by Walker (231) and others that there is considerable confusion and disagreement about the interconnections of thalamic nuclei and particularly the pathways by which unspecific nuclei reach or influence the cortex. Some agreement appears to be emerging gradually from the results of several neurophysiological studies bearing on this problem. In particular those structures in the thalamus which, when stimulated electrically, produce recruiting responses, activation or both in widespread areas are known. Destruction of certain areas eliminates recruiting, natural sleep spindle bursts, and unilateral synchronization of spindle bursts in thalamus and cortex. Some lesions appear to produce distractibility and loss of attention. In the following studies the nucleus ventralis anterior, or at least certain anterior ventral regions, appear to be important as a possible pathway of egress of DTPS influences.

Lindsley *et al.* (163) demonstrated in acute cat preparations that transection of the neuraxis at successively higher levels in the brain stem produced increasing amounts of electrocortical synchronization,

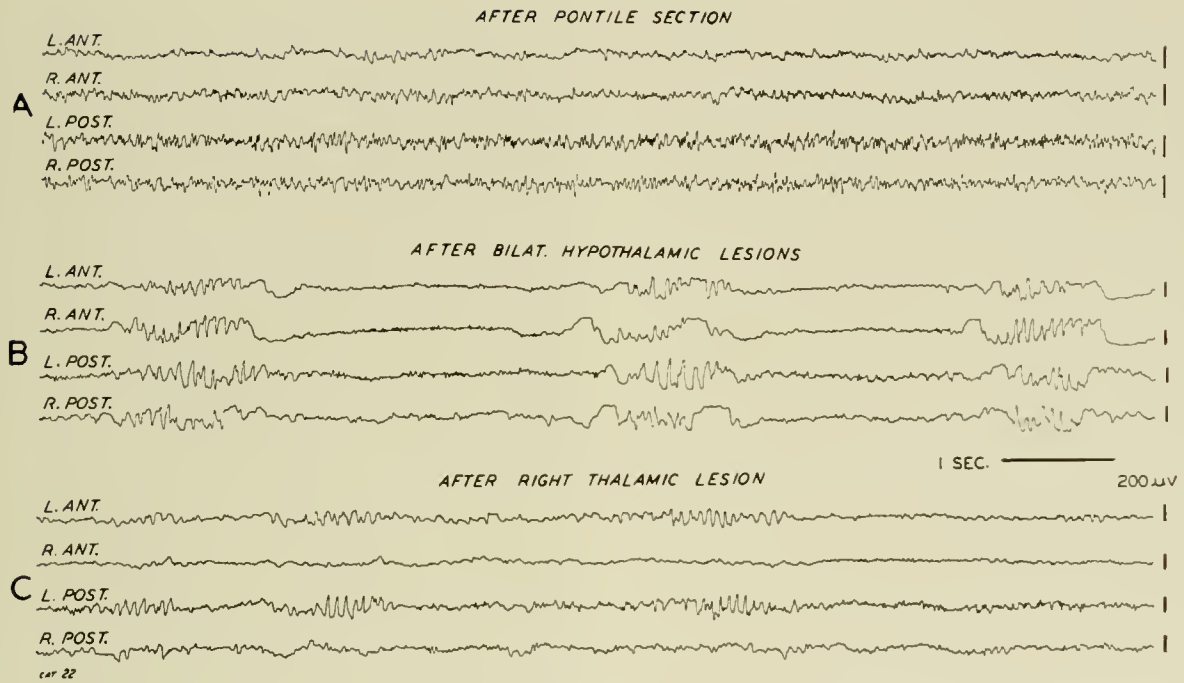



FIG. 6. Cat with transection at the pontobulbar junction shows partially activated EEG (*A*), loss of activation and replacement with spindle bursts after caudal hypothalamic lesion (*B*), and ipsilateral loss of spindle bursts in the right hemisphere of the cortex following lesions to the right thalamic regions (centromedian, intralaminar and ventral nuclei) which previously gave bursts synchronized with those of the cortex. [From Lindsley *et al.* (163).]

with slow waves and spindle bursts. When a lesion was made so as to transect the ARAS bilaterally in the region of the posterior hypothalamus, periodic and prominent spindle bursts appeared in all cortical regions. These spindle bursts occurred simultaneously in the cortex and in certain nuclei of the thalamus. They were observed primarily in the centromedian nucleus, in the lateral intralaminar nuclei, and in the lateral parts of the ventralis lateralis and ventralis anterior. Unilateral decortication abolished the spindle bursts in the ipsilateral thalamic regions previously showing them, but synchronous spindle bursts remained in contralateral thalamus and cortex. Similarly, as shown in figure 6*C*, lesions restricted to the thalamic nuclei showing spindle bursts abolished the synchronized cortical bursts on the ipsilateral side but did not interfere with the simultaneous bursts in the thalamus and cortex of the opposite side. Thus, there is evidence that unspecific nuclei of the thalamus, even though they may not have direct connections with the cortex, nevertheless maintain a temporal synchrony with it.

It is of interest that these nuclei showing spindle bursts in synchrony with the cortex were also part of the complex of nuclei shown by Morison & Dempsey (179), Starzl & Magoun (222) and Starzl & Whitlock (223) to produce widespread cortical recruiting responses. It is further of interest that nuclei of the ventral complex, especially ventralis anterior, were involved in the corticothalamic spindle bursts, for several studies seem to indicate that the nucleus ventralis anterior may be a common point of egress for impulses from the unspecific nuclei (142, 223, 228). More recently Eidelberg *et al.* (69) concluded that the nucleus ventralis anterior serves as a relay station for the nonspecific thalamic projections, since lesions in no other part of the thalamus, or the septum, blocked recruiting responses as did lesions in the ventralis anterior. Chow *et al.* (48), concerned with more massive lesions in the rostral thalamus, found that barbiturate bursts and recruiting responses were degraded by anterior thalamic lesions. Although some temporary behavioral changes were noted, none persisted beyond 2 to 8 weeks, and cats with rostral thalamic lesions could learn a visual form discrimination, suggesting that there was no marked

deficit of attention. These authors feel their results indicate that barbiturate bursts and recruiting responses are more closely related to sleep spindles than to alpha rhythm. In each of these three instances of commonality in the burst pattern, there is not only a tendency for induced sleep, but the point on the human EEG and sleep-wakefulness continuum where consciousness is greatly reduced or lost often corresponds with this type of electrical activity.

In general, behavioral studies before and after lesions have so far contributed little to our understanding of the role of particular nuclei of the DTPS, especially so far as attention and awareness are concerned. This is due partly to the inability to make precisely delimited lesions without affecting other systems, and partly to inadequate behavioral assessment methods. Freudenberg *et al.* (81) observed some distractibility in the monkey after unilateral destruction of the dorsomedial thalamic nucleus. Chow (47) found no outstanding deficits in learning or behavior in the monkey after pulvinar and combined pulvinar and dorsomedial nuclei lesions. In cats Schreiner *et al.* (210) observed increased hostility and aggressiveness following destruction of dorsomedial nuclei, but Pechtel *et al.* (191) were less certain of this in follow-up studies. Ingram (123), summarizing experiments done with Knott and others, reported that bilateral destruction of dorsomedial thalamic nuclei slows performance rate and retards learning in the cat, but that lesions of the nucleus centromedian had no such effects. The results of Brierley & Beck (39) in the cat and monkey indicate that restlessness and distractibility follow bilateral dorsomedial nuclei lesions in the monkey, but that bilateral lesions in the nuclei composing the anterior complex have relatively little effect upon behavior. Because of the role of these nuclei in the recruiting response mechanism, and because their stimulation often induces changes in the level of consciousness, as well as electrocortical arousal and behavioral arousal under some conditions of stimulation, and sleep under others, it appears that there is need for further restricted lesion studies of the mid-line and intralaminar nuclei and the nucleus ventralis anterior relative to attention, perceptual discrimination and learning.

Observations of behavior resulting from stimulation of the midbrain reticular formation, medial intralaminar thalamus, ventrolateral thalamus, dorsomedial thalamus and rhinencephalon have been made by Monnier & Tissot (177) in the rabbit. High-frequency stimulation of the reticular formation produced the characteristic arousal and alerting responses behaviorally and desynchronization electrocortically, but with synchronization in the rhinencephalon which showed rhythmic 5 to 7 per sec. waves during the cortical activation. Both behavioral and electrocortical arousal reactions could also be produced with low-frequency stimuli of 4 per sec. in the reticular formation, but with much longer latency, occurring toward the end or even after stimulation. This suggested to these authors a dual mesencephalic reticular system for arousal and alerting, one of short latency and one of very long latency. Tissot & Monnier (225) and Monnier *et al.* (176) have observed a similar dichotomy from stimulation in the medial thalamus, again with short and longer latency (6 to 12 msec. and 20 to 36 msec.). They identify the early response mechanism as ergotropic and related to the reticular system because it is a quick-acting system, with persistent response, which increases with wakefulness and is enhanced by ergotropic alerting drugs. The other slower response mechanism they identify as trophotropic in type because it decreases during arousal, is facilitated by tranquilizing drugs and is identical with the thalamic recruiting system. Microelectrode records from cortical neurons seem to bear out their contention that these two systems anchored in the medial intralaminar regions of the DTPS are antagonistic and bear a somewhat reciprocal relation to one another. Tissot & Monnier (225) believe that this reciprocal antagonism probably plays an important role in the regulation of vigilance and consciousness.

### *Interaction of ARAS, DTPS, STPS and Neocortex*

Although neuroanatomical and neurophysiological details are far from complete, the foregoing survey of neurophysiological experiments bearing on the ARAS and DTPS seems to support certain generalizations concerning sleep, wakefulness, consciousness and attention. The ARAS is a system promoting wakefulness. Its origins are in the reticular formation of the lower brain stem, situated strategically at the crossroads of afferent and efferent systems from which it receives collaterals. Its upward extensions permit it, either directly or indirectly, to influence the neocortex in a diffuse manner, and in turn to be influenced by the neocortex through widespread corticifugal connections.

When excited through its afferent collaterals or by corticifugal connections, it is capable of arousing a sleeping animal or alerting a wakeful one. In so doing it modifies the electrical activity of the cortex, shifting

the pattern from one characteristic of sleep with large slow waves and spindle bursts to one of low-amplitude fast activity or, in the case of wakefulness, further differentiating the pattern by desynchronization and activation. If its activity is reduced by anesthesia, or if its upward extensions are cut off from the lower brain-stem portion of the reticular formation, a state of somnolence and unconsciousness ensues, despite the fact that sensory messages may still traverse the classical pathways to the thalamus and cortex. Even under light to moderate barbiturate anesthesia such messages are ineffective so far as perceptual discriminations are concerned without the influence of the ARAS.

The routes of the upward extensions of the ARAS are as yet uncertain, but it is believed that one takes an extrathalamic course, possibly by way of the subthalamus and internal capsule, and that another passes by way of the thalamus, presumably terminating in the mid-line and intrathalamic nuclei, in the reticular nucleus or in both. Whatever its influences may be in the thalamus, upon DTPS or STPS, its ultimate effects upon the cortex are not to be denied. Its extrathalamic influences are believed to be relatively rapid ones and concerned with general arousal, its thalamic influences are more likely concerned with gradations of alerting to attention and may be related to scanning or modulating influences affecting the STPS, or the integration of STPS information by the DTPS.

The functions and relations of the DTPS are still less clear than those of the ARAS. Some of the nuclei composing this system apparently serve intrathalamic association functions, others interact with the cortex, basal ganglia and rhinencephalic structures. Those in direct or indirect connection with the neocortex appear to be capable of electrocortical activation or desynchronization, after the manner of ARAS function. Another function appears to be the regulation of so-called spontaneous cortical rhythms, control of after-discharge and after-potentials following STPS action, and the regulation of temporal synchronization between thalamus and cortex in a fashion permitting the development of cortical recruiting waves, sleep spindles and other rhythmic phenomena of the cortex, perhaps including the alpha rhythm of the normal resting EEG. As such it may control waxing and waning cycles of excitability in the cortex which could regulate rapid shifts of attention (159). Evidence of such excitability cycles has been put forward by Bishop (24), Bartley & Bishop (17), Chang (44–46), Lansing (153) and others.

INHIBITION AND FACILITATION VIA THE RETICULAR FORMATION. Cortical or reticular stimulation has been shown in several experiments to be capable of producing inhibition (63, 84, 89, 92, 94, 100, 141) or facilitation (36, 66, 161) in one or another of the several sensory systems. Inhibition has been demonstrated from the first synaptic relay to the final relay in the thalamus. To take one example, Hernández-Peón *et al.* (107) have demonstrated that stimulation of the mesencephalic reticular formation depressed or abolished the secondary wave of the evoked potential in the nucleus gracilis induced by stimulation of the dorsal column. They also demonstrated that the second component of the evoked potential in the trigeminal nucleus, elicited by stimulation of the infraorbital nerve, could be enhanced by destruction of the midbrain tegmentum, thus demonstrating release of tonic inhibitory influence from the reticular formation. Finally, and important in relation to other recent experiments dealing with the visual system, they show that photically evoked potentials in the optic tract, lateral geniculate body and visual cortex could be significantly modified by reticular stimulation. In both the lateral geniculate body and in the visual cortex the second component of the evoked complex was depressed during and following brief reticular formation stimulation. The optic tract showed both depression and potentiation, believed to result from two antagonistic effects of centrifugal discharges upon retinal synapses.

In contrast to the above results, recent studies (36, 37, 66, 161) have shown facilitatory effects in the visual cortex and in the lateral geniculate bodies as a result of reticular stimulation concurrently with excitation of the visual pathways by photic or optic nerve stimulation. Improved resolution or temporal facilitation in the visual cortex of the cat has been reported by Lindsley (161) following reticular stimulation. Figure 7 shows a single evoked potential in the visual cortex (VC) to a pair of light flashes 50 msec. apart, but after reticular formation stimulation the same pair of flashes resulted in two evoked potentials. The dual response continued for about 10 sec. and then the response became single again. Another kind of facilitation has been described by Bremer & Stoupel (36, 37) and by Dumont & Dell (66). These investigators report increased magnitude of evoked potentials in the lateral geniculate bodies and visual cortex to optic nerve stimulation which followed stimulation of the mesencephalic reticular formation. The former also observed enhancement of cortical

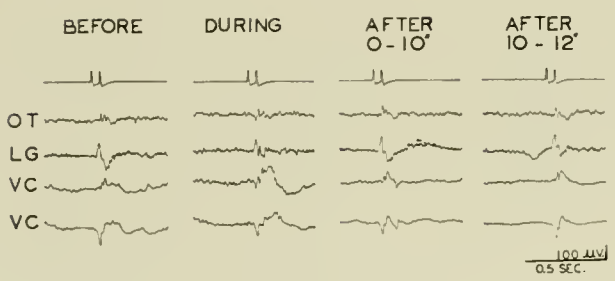



FIG. 7. Limitation of the cortex in a cat in responding to closely spaced brief light flashes, but facilitated by reticular stimulation. Two 20-μsec. flashes of light separated by 50 msec. and presented once per sec. are responded to as one by the visual cortex (*VC*) until after a 5-sec. period of reticular formation stimulation. For 10 sec. thereafter two evoked potentials appear, and then return to the original single response. This is an example of temporal facilitation. *OT*, optic tract; *LG*, lateral geniculate body; *VC*, visual cortex. [From Lindsley (161, 162).]

potentials to optic nerve stimulation when the centromedian nucleus of the DTPS was stimulated.

Thus we see that ARAS and DTPS interaction with STPS, or STPS cortical effects, is capable of facilitation, but also in some instances inhibition. Similarly, we have noted that centrifugal discharges, due to cortical or reticular stimulation, produce inhibition in peripheral sensory relays and in a few instances give rise to potentiation of specific responses. What is the role of these mechanisms? Do they provide a means of selective control of sensory input such as might seem to be required for restricting attention?

### *Cortical Interaction of Specific and Unspecific Influences*

The role of the specific (STPS) and unspecific (ARAS and DTPS) sensory systems is by no means clear at the present time, and yet it is certain that they must interact if incoming sensory messages are to be decoded and integrated with past experience in meaningful ways. One important indication of the necessity for this is the fact that perceptual discrimination will not occur in the absence of ARAS influence, when blocked by lesion or anesthesia, or even when reduced as in natural sleep, despite the apparent delivery of sensory messages over the specific system as indicated by unimpaired cortically evoked potentials. Such interaction may be conceived in at least two general ways, one involving individual units and their local relationships, the other involving more general relationships of receptive and association zones. With regard to the first of these there have been hypotheses about the axosomatic terminations of STPS upon cortical units, and axodendritic terminations of the more diffusely arrayed ARAS and DTPS influences. The existence of interneurons between diffuse projections and cortical units has also been proposed (197). Although far from complete, microelectrode studies of cortical unit activity is beginning to supply some information on these questions.

With regard to the grosser areal relationships, there is already some interesting evidence. Starzl & Magoun (222) and others have observed that diffuse thalamic projections, as exhibited by the cortical areas in which the most prominent recruiting responses can be elicited, tend to be limited to the associational cortex of the frontal, cingulate, orbital and suprasylvian portions of the hemisphere in the cat, but with overlapping of the motor fields. Jasper *et al.* (133) demonstrated a more labile topographic organization, and under more specific conditions observed that recruiting responses extended also to sensory receiving areas. Dempsey & Morison (59) originally observed that primary sensory areas, and particularly auditory and visual areas, developed poor recruiting responses. When they applied repetitive low-frequency stimulation to specific thalamic nuclei and adjacent regions, they observed another, but perhaps related, phenomenon which they called 'augmenting' responses in the cortical zones of specific projection (61, 180). Augmenting responses have a shorter latency than recruiting responses, and can coexist with spontaneous waves and spindle bursts; recruiting responses on the other hand displace spontaneous waves and spindle bursts, suggesting that they involve some of the same cortical elements.

There is obviously a need to distinguish more clearly between, or to identify common features among, the following: spontaneous waves of the cortex, spindle bursts, recruiting waves, sensory after-discharge (44), secondary responses (62, 75), and self-sustained and cortically spreading or corticocortical responses (4, 202). Not only must these be distinguished in terms of the elements contributing to them, but also the areas from which they arise. The functions which these areas subserve must also be more clearly delineated.

The significance of these areas, their local functions and their thalamic counterparts might derive some meaning if viewed in the light of the phylogenetic interpretation and approach suggested by Herrick & Bishop (108) and Bishop (26). From a phylogenetic viewpoint Bishop sees the reticular system as a series of segmental, level-to-level integrating systems. The reticular formation is one of these, the links between

thalamus and cortex constitute others, and within the cortex there are still others. Both specific and nonspecific systems get duplicated and reduplicated in the highest forms of evolutionary development of the brain. Thus a sense mode may be represented by three primary receiving areas and two or more association areas. The reticular formation, the region of the centromedian nucleus and the older associational cortices are areas in which one might expect convergence of sensory influx with multiple sensory representation, as Albe-Fessard *et al.* (9, 10) have found recently. The intermixture and convergence of the older and newer specific, nonspecific and associational systems is undoubtedly responsible for some of the difficulty and confusion which exists currently in attempting to identify and separate the fields of primary and secondary evoked responses as well as other patterns of activity which exist on the cortex. According to Bishop, in primates newer association areas act as facilitators or modulators of older association areas which he refers to as thalamocortex. It is in this thalamocortex that he believes the two sensory systems, specific and unspecific, converge. Could it be here that a temporal coincidence and convergence makes possible perceptual identification and discrimination? If the phylogenetic concept of a 'reticular system' is one extending from cord to cortex, and this integrating network is connected throughout by multisynaptic junctions, but with segmental links with some hierarchical ordering, then throughout the neuraxis it becomes a dominating influence for afferent and efferent regulation, as foregoing sections of this chapter have indicated. But wakefulness, attention and discrimination are probably some of the principal functions of major segments of 'the reticular system,' as represented in the reticular formation of the lower brain stem, the unspecific nuclei of the thalamus and the associational areas of the cortex, respectively.

The recent and important studies of Buser *et al.* (41, 42) and of Albe-Fessard *et al.* (9, 10) suggest the existence of not only dual, but triple thalamocortical systems, and convergences within the thalamus and cortex of multiple sensory representations, just as Bishop's concept would seem to require. Using chloralose anesthesia or curarized preparations, Buser *et al.* (41, 42) have found what they call secondary associative responses in two separate association zones in the auditory and in visual fields in response to auditory and visual stimuli. These responses are enhanced by chloralose, but are blocked by barbiturates. This would suggest that they originate in or are a part of a reticular system. They do not depend upon their corresponding primary projection areas which can be removed or depressed by drugs without loss of response in the well-defined cortical association areas. Destruction of the reticular formation at a mesencephalic level did not abolish these secondary responses which suggest that the mechanism is not a part of the ARAS nonspecific system, but does not rule out the DTPS.

The secondary association responses are confined to the association zones and can be distinguished from primary responses by their longer latency and greater duration. With respect to alerting and wakefulness, it is especially interesting to note that the association irradiation responses are best observed not during marked activation or arousal, but during lower degrees of vigilance, with only slight activation or alertness. Since these responses can be produced by stimulating the specific thalamic nuclei (medial and lateral geniculate bodies) for audition and vision, or from the lateral-posterior nuclear group of association nuclei, it has been proposed that they depend upon 'collateral' elements which branch from the primary sensory pathway and enter the thalamic association nuclei. Stimulation of the primary nuclei for audition and vision gives rise to both primary and associative responses in the cortex. The appearance of these responses in a certain level of wakefulness and alertness implies that they are related to the process of attention, and may have still further significance so far as perception is concerned.

The observations of Albe-Fessard *et al.* (9, 10) indicate that stimulation of different limbs of the cat and monkey, irrespective of location, causes evoked potentials in the centromedian nucleus and in parietal and frontal association areas, both ipsilaterally and contralaterally. Such nonprimary responses, elicited by somatic stimulations of different origins, have not previously been described. Their latencies and durations are greater than those of primary responses. However, they are individualized with silent zones between. The outstanding characteristic is the convergence of stimulations upon a given cortical locus, with all somatic areas having representation in this convergence response. Stimulation of the centromedian nucleus will cause responses in the superior frontal gyrus, but with latencies too long to suggest direct projections.

MICROELECTRODE STUDIES. The response of individual cortical units provides a more detailed evaluation of specific-unspecific interaction. Jung *et al.* (137) have discovered several types of units in the visual cortex. Some show no reaction to light (A neurons); others

show reciprocal inhibition and activation (B, C, D and E neurons). Of particular significance to the problem of interaction being considered here is the fact that there is a convergence of specific and unspecific systems upon the same cortical neurons. Jung's group (7, 51, 137) has shown that the mode of discharge, and the number of light-responsive neurons is altered by stimulation of the nonspecific system. They have found also that most neurons are subject to joint influence in the form of facilitation, inhibition and occlusion. Furthermore, thalamoreticular stimulation increases the maximum frequency with which visual cortical neurons can respond to flickering light. The flicker-fusion rate of individual cortical neurons can be raised considerably by thalamic or reticular stimulation. In contrast to these results, Jasper (129) and Li *et al.* (157) have not been able to detect cortical unit spike discharges, except by stimulation of a specific afferent system. However, they do record an intracortical slow negative wave upon which the spike response of a single unit may be superimposed; and during repetitive stimulation of the nucleus centralis lateralis, multiple discharges of the same unit may be superimposed upon the resulting slow-wave recruiting responses. This undoubtedly means that facilitation of the unit has taken place due to stimulation of the unspecific system. Thus their results, though not strictly in accord with those of Jung's group, may nevertheless indicate some of the same kinds of influences.

Jung *et al.* (137) point to a parallel between the response of individual cortical neurons to flickering light at fusion level and above, when accompanied by stimulation of the ARAS, and the fact that human fusion level may be elevated by increased attention and alertness. They state that: "Activation and increased frequency of cortical neurons in response to peripheral stimulation after excitation through the nonspecific system thus finds a parallel in subjective experiences and suggests a possible neurophysiological mechanism for the regulation of attention."

These workers believe that the nonresponding A neurons constitute about half of the cortical neurons in the optic cortex. The A neurons are thought to receive their activation not from the specific visual relay nuclei, but from association fibers or the medial thalamic nuclei. They look upon them as serving a stabilizing background function which is capable of regulating and adjusting the excitation level in the cortex. This may serve a protective function in the case of massive, seizure-like discharges, or it might serve an attention-regulating function under lesser and more differential stimulation. Thus interaction of ARAS and DTPS with STPS at the level of the cortex might play a significant role in specific alerting and attention. What controls and regulates the specific shifts of attention still remains a problem. Is this a mass influence imposed by ARAS or DTPS, or is there a certain degree of topographical representation; if so, what particular portions of the reticular formation and what particular nuclei of the DTPS are involved? Jung and fellow workers speak of A neurons acting like interneurons which might be both inhibitory and facilitatory in their influence upon other neurons subserving STPS functions.

Jasper (129) observes that a single cortical unit will respond at a higher frequency if preceded by a conditioning shock to the unspecific system, but reports also that from extracellular recordings he has found certain units which will manifest inhibition or facilitation by either unspecific or specific intervention. He calls attention also to the possibility that unspecific influences may affect the excitability of the cells possibly by changes induced upon the dendrites. This might suggest that the unspecific system (ARAS or DTPS) could have a modulating influence upon the excitability of specific cortical synapses. Again the question may be raised, which synapses and by what control? At the moment the possibilities are manifold. More and more specific mechanisms are being demonstrated which add flexibility to the means of control and at several different levels of sensory influx from receptors to cortex, but the manner in which the control is exerted still remains elusive. Is there sufficient topographic representation in the reticular formation or the nonspecific nuclei of the thalamus to accomplish this? Can the degree of differentiation of individual units already demonstrated there (11, 12, 207) be modified and regulated sufficiently by conditioning, learning and habituation? The next section provides some partial answers to such a question.

### *'Habituation' and Attention*

As was pointed out above in connection with the work of Jung's group, approximately 50 per cent of the cortical units studied by microelectrodes in the visual cortex of the cat were unresponsive to light stimulation upon the retina. This group of neurons they looked upon as having a stabilizing influence upon activity in the visual cortex, and perhaps playing a role in visual response mainly under certain kinds of conditions in which arousal, alerting and attention were involved. It is interesting that Erulkar

*et al.* (72) have observed a similar thing in connection with the auditory cortex of the cat where they find that about 34 per cent of the units isolated by microelectrode methods could not be activated by sounds. Galambos and collaborators (119) in studying single-unit responses of the auditory cortex of unrestrained and unanesthetized cats have also encountered units which are unresponsive to sounds, unless the cat is 'paying attention' to the sounds. They have referred to these as 'attention' units since they are so obviously involved only in response to sound when the sound commands the attention of the animal. They found that about 10 per cent of the units examined were units which responded only when attention was simultaneously manifest by the animal's behavior, such as turning of the head toward the source of the sound, and appearing to be alert and attentive. In Pavlovian terminology this might be called an 'orienting response' or orienting behavior.

Such attention units characteristically would not respond to clicks, tones or noises from a loud speaker on repeated tests, although a new tone or noise might evoke a response the first few times it was presented. A unit might respond briskly to the appearance of the experimenter and to certain unique stimuli which attracted the attention of the cat. For example, the voice of the experimenter, squeaks of a toy mouse, scratching sounds, hissing noises or tapping on a table were effective in causing a unit, otherwise unresponsive to repeated noises, to discharge. Clicks from a loud speaker which were ineffective in firing a unit would do so the moment the experimenter pretended to tap the loud speaker which produced the clicks and thus drew the attention of the animal to the source of the clicks. Hence it was evident that such units, presumably 'adapted' or 'habituated' by repetition, could regain functional status by some additional reinforcement or 'disinhibition' brought about by an addition or slight change in the stimulating situation. This change would appear to be related to the ARAS or DTPS rather than STPS. Galambos and fellow workers conclude "that the neural processes responsible for attention play an important role in determining whether or not a given acoustic stimulus proves adequate. Unfortunately attention is an elusive variable that no one has yet been able to quantify. It may be that studies in which cortical unit activity is examined during the course of conditioning and learning will illuminate these matters."

Earlier Hernández-Peón *et al.* (106) demonstrated how 'attention,' in unanesthetized cats with electrodes implanted in the cochlear nucleus, could influence the response of the cochlear nucleus to clicks. Figure 8 shows a regular and uniform response from the cochlear nucleus to clicks when the cat is resting and not apparently attending specifically to the stimulus (the obverse of certain cortical units mentioned above which responded only when the cat was attentive). When two mice in a glass jar are presented and the cat's orientation and attention is obviously focused upon them, the response of the cochlear nucleus to clicks is greatly suppressed. Olfactory and nociceptive stimuli had similar inhibitory effects upon the auditory response. Finally, when the mice or other distracting stimuli are removed and the cat returns to a resting state, the response of the cochlear nucleus returns to its original magnitude. Here is an apparent example of sensory inhibition imposed upon the sensory pathways of a given modality when another competing modality becomes the object of attention. Such an inhibitory mechanism imposed at various synaptic sites in the sensory pathways suggests that the selective exclusion of certain incoming signals may occur peripherally as well as at the cortex or thalamic levels. However, like the centrifugal negative feed-back system mentioned earlier, of which this inhibitory attention mechanism may be a part, the origin of the effect may reside in the cortex or reticular formation of the lower brain stem. The important point would seem to be

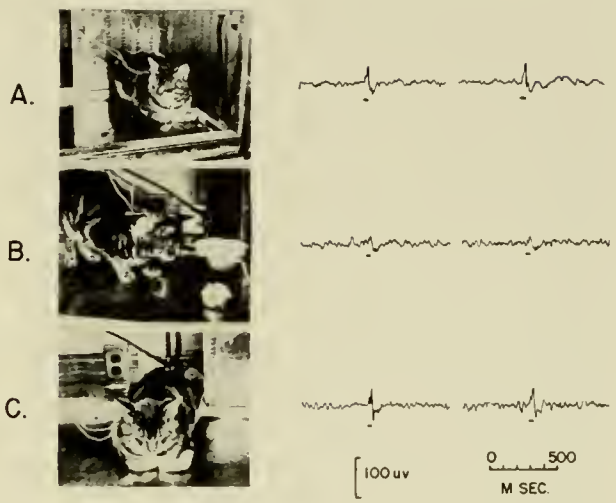



FIG. 8. Suppression of response in one modality by selective attention in another. Indwelling electrodes in the cochlear nucleus of a cat for recording cochlear potentials to click stimuli. *A:* cat relaxed, cochlear response strong. *B:* cat responsive and attentive to two white mice in jar, cochlear response weak. *C:* cat relaxed again, cochlear response to click restored. [From Hernández-Peón *et al.* (106).]

that 'attention' or the process of exclusion of certain sensory messages in favor of others may begin at various levels of the sensory input as well as at the thalamic and cortical levels. By decortication, or by lesions or transections at critical points in the nervous system it should be possible to determine whether the reticular formation, the cortex or both are essential to this particular form of sensory inhibition.

Jasper *et al.* (134), in examining the unit firing patterns in the motor cortex of monkeys during conditioned avoidance responses, found inhibition of unit discharge was more common during the CS-CR interval but observed increased firing during the CR itself. To an unreinforced differential stimulus there was decreased unit firing which they interpreted as habituation rather than active inhibition. During the light-shock avoidance conditioning they found in the parietal and occipital cortex more evidence that the units would respond to the temporal patterning of the CS flashing light and that these were comingled with secondary evoked responses to the somatic unconditioned stimulus. Occipital evoked potentials were strong through the CS-CR interval but were reduced sharply just preceding the CR, which they interpret as related to a shift in attention, as previously described by Jouvet & Hernández-Peón (136). In tentative conclusions concerning these preliminary experiments, Jasper and colleagues propose that "specific sensory or motor systems of the brain are not primarily involved in the neuronal circuits critical for the conditioned response" and that "search should be directed to non-sensory-motor cortex and probably to centrally situated neuronal systems of the brain stem which receive convergent patterns of impulses from many sources." In this respect the work of Buser, Albe-Fessard and others mentioned above would seem to provide clues concerning convergence areas. Jasper and colleagues have emphasized habituation and conditioning as contrasting and antagonistic processes, pointing out that conditioning involves elimination of all irrelevant stimulus-response reactions which are not reinforced. This they call habituation. Before the CS-CR pattern is established by appropriate reinforcement, they imply that attention of a specific nature must be focused upon the correct sequence.

With regard to alerting responses and habituation, Jasper *et al.* (134) observed that cortical cells might fire quite actively during drowsiness or sleep; some firing only during bursts of slow waves would cease to fire when the overall EEG indicated activation or arousal patterns. Still other units would fire very actively when the animal was awakened or aroused, but would decrease their rate of firing during continued alert or excited states. The habituation of such arousal responses has been studied by Sharpless & Jasper (213), using the EEG as an indicator as well as behavior.

Sharpless & Jasper discuss the nature of habituation, and describe it as differing from sensory adaptation and nerve accommodation in its temporal characteristics. Like learning, it seems to be represented in the central nervous system by some form of plasticity. It may develop even with long intervals between stimulus presentations and may persist for hours or days. Habituation to a specific stimulus quality or intensity will give way to a unique or novel one, or to one differing in intensity only. It seems to be characterized by the fact that a particular reaction or response to a specific stimulus repeated at intervals over a period of time will eventually fail to occur unless reinforced in some manner by a painful, rewarding or otherwise effective stimulus for that response. In this respect it may resemble extinction of a conditioned response, but in other respects it is different. It may be restored immediately upon a shift to another stimulus mode or following a change in intensity in the same sense mode, even though the original stimulus is again employed. These authors liken this negative adaptation or habituation to a decrease of alertness or attention such as is found in everyday tasks like those described at the start of this chapter, where repetition, monotony, boredom and the like are involved. It is similar also to the disappearance of the 'orienting reflex' of Pavlov or the 'startle response' of Landis & Hunt (152) which succumb to repetition.

Using the arousal reaction of the EEG (shift from high-voltage, synchronized slow waves of sleep to low-voltage, desynchronized fast waves of wakefulness) as a criterion response which disappears upon 20 to 30 repetitions of an arousal tone (habituation), Sharpless & Jasper studied a great variety of characteristics of this phenomenon. They conclude that habituation of the arousal reaction is specific to the quality, modality or pattern of a given stimulus. Two types of arousal reaction were differentiated, a longer lasting one more susceptible to habituation and a shorter lasting one less susceptible. The tonic slow and persistent arousal response is believed to be mediated by the mesencephalic portion of the ARAS; the faster more differentiated arousal response appeared to be dependent upon the DTPS. For specific nonpatterned stimuli the habituation of the activation or arousal response could be detected in the cortex, thalamus and reticular for-

mation, and persisted in the absence of auditory cortex.

This important experiment, in agreement with other studies, suggests that the tonic, longer-lasting arousal reaction which is subject to habituation by selective but less differentiated stimuli may be a part of a general arousal and attention mechanism subserved by the ARAS. With its principal locus in the strategically located reticular formation, capable of monitoring input-output functions, it might be thought of as serving a first order protective, preparatory and adjustive function in the manner suggested by Cannon, Gellhorn, Hess, Ranson and others. The phasic, shorter-lasting arousal reaction, less susceptible to habituation and capable of greater stimulus differentiation and associated less with ARAS than DTPS, would appear to be mediated by a mechanism better adapted to the special alerting and highly selective attention needed for higher forms of discrimination and learning.

In the foregoing experiments, as well as in other recent studies (43, 64, 85, 101–103) bearing on arousal, alerting, attention, habituation and conditioning, it has become evident that a complex of interrelated mechanisms is involved. Specific afferent pathways of communication must be maintained, but it appears necessary also for these to have several points of confluence and convergence within the central nervous system. Specific sensory pathways conduct messages from a variety of specialized and widely dispersed receptors to special destinations in the cortex and elsewhere. Interposed in these pathways at various strategic locations are relays or synapses which are subject to centrifugal influences which regulate and control the sensory influx.

Attention, perceptual discrimination, conditioning and learning require, however, more than the deliverance of specific messages to certain segregated locations, for information from several diverse sources must be brought together if elaboration, correlation and integration are to occur. In conditioning, as we know, one sense mode may come to substitute for another in effecting a response, and in order to accomplish this there must be points of confluence and convergence. The reticular formation of the lower brain stem, the unspecific nuclei of the thalamus and the association zones of the cortex appear to be centers of convergence, as does also the hippocampus. These convergence centers, although interposed at different levels of the central nervous system, appear to be mutually interactive and share some functions in common.

How the separate and conjoined sensory influences in these regions of the brain provide the conditions of discrimination, retention, plasticity and modifiability we know to exist will long be the subject of intensive study, but some progress is being made as the results reported here attest. However, neuroanatomically, neurophysiologically and behaviorally, we have barely scratched the surface and much remains to be done. So far in this chapter we have considered mainly the neurophysiological and electrophysiological studies which have revealed new mechanisms and new concepts of brain function. We shall now turn to another class of electrophysiological events, the electroencephalogram (EEG). Of more global character it represents ongoing activity in the brain recorded at a distance from the surface of the scalp.

## THE ELECTROENCEPHALOGRAM IN SLEEP AND WAKEFULNESS

### *Characteristics of the EEG in Wakefulness*

Hans Berger, a German neuropsychiatrist, is aptly called the father of electroencephalography. In his first few articles (19–22), he described the basic types of electrical activity generated in the brain of human subjects and recordable from the surface of the scalp. These are described by Walter in Chapter XI of this *Handbook*.

The normal waking EEG is characterized by a prominent alpha rhythm composed of waves of 8 to 12 per sec. and about 30 $\mu$v. on the average. The persistence, rhythmicity and regularity of the alpha waves vary from individual to individual. In a state of quiescence with eyes closed the alpha rhythm is more or less continuous but often shows amplitude modulations. Like the ARAS, the alpha rhythm is affected by all types of sensory stimulation. About two fifths of a second after an unexpected stimulus, the alpha waves block and the EEG may remain in a state of activation with only low-voltage fast or base-line activity for several seconds or longer until the subject has become accustomed to the stimulation. After a few repetitions of the stimulus the alpha blockade lasts only about 1 sec. before the waves return, and after a number of repetitions habituation may set in with the result that no blocking or suppression of the alpha waves occurs. Visual stimulation is less susceptible to habituation than auditory or other types.

Berger believed the alpha blockade resulted from the focus of attention upon a specific sense mode with generalized inhibition spreading to other sense zones.

Adrian & Matthews (6) and more recently Adrian (5) also adhere to the view that attention to a stimulus or even attempts to see or hear a stimulus not actually present is responsible for the disappearance of the alpha waves and their replacement with low-amplitude fast and irregular waves. This type of reaction we now call an 'activation' or 'arousal' response and attribute it to increased activity in the reticular system, including the ARAS and DTPS. However, it may also be a function of selective attention since the waves block with sensory stimulation, mental arithmetic, or attempting to visualize a scene or recall a melody.

We need measures of activation and attention, and the EEG offers promise in this regard. Behaviorally a person may feign sleep and deceive an observer but not a trained EEG observer, for his record would show alpha waves or some degree of activation or arousal responses. He could not feign sleep characteristics. If a person is supposed to be awake and alert and fixating an area in order to make observations, one would expect the EEG record to show either a condition of activation with low-amplitude fast waves or alpha waves if he has become somewhat habituated to the condition. If either picture shifts to slow and sporadic alpha waves or to even slower delta waves, or mixtures of the two, one can predict quite reliably that the subject is not alert and attentive, but on the contrary is drowsy. Usually the subject will admit dosing or drowsing if questioned at that time; or if a stimulus for reaction-time measurement is given at such a time, it will either be missed entirely or the reaction will be slow.

Although the alpha rhythm averages about 10 waves per sec. in older children and adults, it has a much lower frequency in very young children. During the waking state in newborn infants there is no organized or persistent alpha rhythm over the sensory areas of the brain. By 3 or 4 months the sensory zones develop a persistent alpha rhythm of about 3 or 4 waves per sec. These increase to about 5 or 6 per sec. at 1 year of age and by 10 or 12 years of age have reached the adult frequency of 10 per sec. Figure 9 shows the longitudinal development of the occipital alpha rhythm during the waking state in the same child from infancy to adulthood. Prior to the development of an alpha rhythm it is difficult to attract and maintain the attention of a child of 1 or 2 months of age. After the child develops an occipital alpha rhythm, the waves can be blocked by a visual stimulus, indicating that activation via ARAS is possible. Before the infant develops an alpha rhythm in the occipital area,

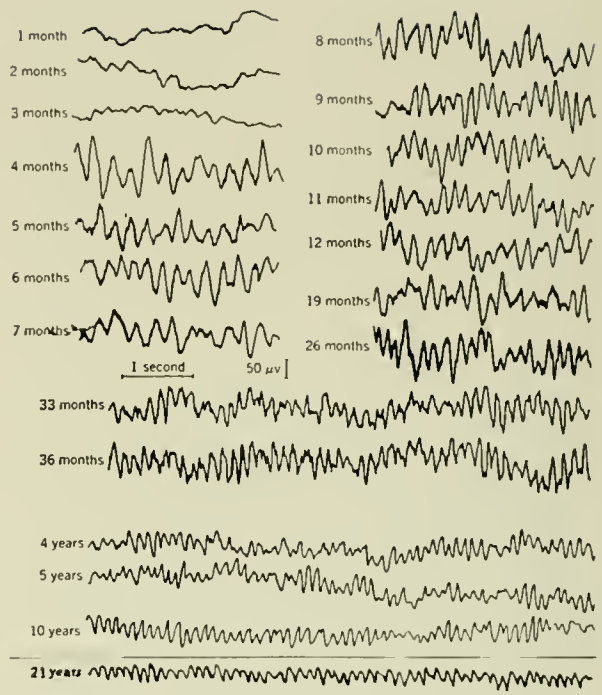



FIG. 9. Longitudinal development of occipital alpha rhythm in the same subject from early infancy to 21 years of age. Alpha rhythm typically appears in a persistent pattern by the third or fourth month, with a frequency of 3 to 4 waves per sec. By 1 year the frequency is 5 to 6 per sec., and by 10 years it may attain the adult average frequency of about 10 per sec. Note that as frequency increases, voltage diminishes.

repetitive photic stimulation will induce a rhythmic activity in synchrony with the stimulus, but only in the immediate range of the natural alpha rhythm which would appear at 3 or 4 months of age. There is some reason to believe that the alpha rhythm is maintained or synchronized by unspecific nuclei of the DTPS but is capable of activation by either ARAS or DTPS. Thus the establishment of a rhythm in a young infant must mean that the sensory zone involved has taken on a new functional role. The convergence of specific and unspecific influences upon a cortical zone in which rhythmicity and activation properties have been attained indicates that perceptual capacity is also now available. This extension of sensory and perceptual capacities to the cortex implies that a new level of consciousness has been attained as well. Attention, perceptual discrimination and consciousness are matters of degree, level, temporal relations and perhaps other factors. One wonders about the young infant with slow alpha waves and slow development of an evoked potential following stimulation. To what

extent does the slower time constant of these systems determine the speed of attentive adjustment, of perceptual discrimination and so forth? With an alpha frequency of 5 per sec. at 1 year of age, alpha blockade time or latency is twice as long as it is when the alpha frequency has attained 10 per sec. at 10 years or later.

At the present time beta waves of 18 to 30 per sec. and under 10 $\mu$v. on the average, and gamma waves of 30 to 50 per sec. and even smaller, hold little promise for use as analytical devices. Both are easily confused with muscle potentials and other low-level artifacts. Neither is responsive to sensory stimulation directly as is the alpha rhythm. Beta waves are more easily observed over the frontal half of the head, and over motor and frontal association zones where alpha waves, though present, are not as prominent as posteriorly. Beta waves are said to respond to motor movement.

Theta waves of 4 to 7 per sec. are seen mainly in temporofrontal regions in children but are often associated with behavior disorders or other physiopathological instabilities. Delta waves ranging from less than 1 to 4 per sec. are not seen in the EEG record of normal subjects unless they are drowsy or asleep. Slow and large delta waves are usually considered indicative of pathology or physiopathology.

### *Characteristics of the EEG in Sleep*

The EEG undergoes striking changes in pattern in the transition from wakefulness to sleep, and has become one of the more convenient and reliable ways to assess the state of wakefulness or sleep. Berger (22) observed that alpha waves slow and are reduced in amplitude and eventually disappear as sleep develops. Loomis *et al.* (166–169) studied all-night sleep records and noted not only the abolition of alpha waves as light drowsiness gave way to deep drowsiness, but that a series of distinct patterns emerged as various stages of sleep ensued. In particular they called attention to 12 to 15 per sec. sleep spindles and the appearance of random slow waves as actual sleep began. Growing out of the work of several groups of investigators concerned with the study of stages of sleep (28, 53, 99, 144, 147, 148, 169, 170, 215) came a fairly consistent and systematic picture of the changing patterns in the transition from wakefulness to sleep. Briefly these stages may be described as follows. *Stage A* (*Awake*). Alpha waves are present at the start but diminish in voltage and amount as the subject shows slight drowsiness. *Stage B* (*Drowsy*). Alpha waves diminish still further and vanish leaving the base line relatively flat or with low-voltage fluctuations and sporadic delta waves. *Stage C* (*Light Sleep*). Fourteen per sec. spindle bursts develop on a random, low-voltage, delta-wave background. *Stage D* (*Medium Sleep*). Delta waves decrease in frequency but increase in voltage and amount; the spindle bursts disappear. *Stage E* (*Deep Sleep*). Delta waves increase in duration, voltage and randomness. The transition stage between *B* and *C* is one of going from fluctuating awareness or deep drowsiness to complete lack of awareness or loss of consciousness. During *Stage C* the subject makes no perceptual discriminations and has no memory for events or sensory stimulations, unless these are intense enough to wake him up. Each of the above stages can be further subdivided on the basis of certain criteria in relation to the EEG pattern as Simon & Emmons (215) have done. The above classification is based mainly on that of Loomis *et al.* (169), Davis *et al.* (53) and Simon & Emmons (215–217), each of whom presents illustrations and detailed descriptions.

The transition from sleep to wakefulness follows a similar though more variable course in the reverse direction. Changes may be more precipitous from one stage to another. With the return of consciousness on waking, alpha waves are present in reduced amount and voltage, and may not assume their regular form and character for some time. Henry (99) found that EEG patterns of individuals on waking tend to be more homogeneous and alike than at any other time. As a few hours intervene after waking, the EEG records take on greater individuality.

Ontogenetically, as shown in figure 10, the EEG sleep pattern emerges with time. These tracings taken at different times from the same child indicate that in light to moderately deep sleep the EEG sleep pattern corresponding to these stages of sleep has not clearly emerged during the first 10 to 15 days, although there are evidences of incipient delta waves and even spindle bursts in the motor region. By 105 days the general pattern of spindle bursts and random slow wave activity is clearly evident, as it also seems to be at about 30 days. The same general type of pattern is also seen at 280 days and thereafter for light to moderate depth of sleep. Others who have studied the EEG of newborn and young infants are Smith (218), Hughes *et al.* (121, 122), Nekhorocheff (184) and Ellingson (71).

### *The Sleep-Wakefulness Continuum*

In attempting to relate the various stages of the EEG pattern to corresponding psychological states

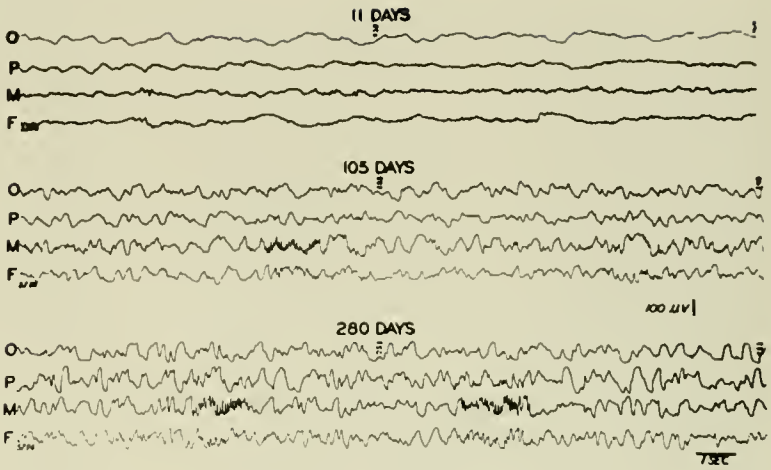



FIG. 10. EEG sleep records in the same child at different ages. The first 10 to 15 days show little activity characteristic of sleep beyond the age of 1 month. Note the incipient slow waves and, in the motor and frontal records near the start, an incipient sleep spindle burst. Records at *105* and *280 days* are composed of slow waves and periodic spindle bursts, and differ little from those of a 1- or 2-month-old child. *O*, occipital; *P*, parietal; *M*, motor; *F*, frontal. [From Lindsley & Ellingson, unpublished data obtained at The Cradle Society, Evanston, Illinois, 1949.]

and their behavioral correlates Lindsley (159) developed the concept of a continuum (see fig. 11 and table 1). Figure 11 shows some of the stages of the normal EEG extending from an activated or excited state with low-voltage fast activity as in arousal or alerted states to deep sleep with large, random slow waves. During a relaxed state of wakefulness more or less continuous, amplitude-modulated alpha waves are characteristic. In drowsiness alpha waves diminish and low-amplitude slow waves begin to appear. In light to moderate sleep spindle bursts and slow waves are conspicuous and in deep sleep only large and random slow waves are seen.

Table 1 lists the full range of EEG stages against a behavioral continuum, and the corresponding states of awareness and behavioral efficiency. It should be noted that the most aroused or excited state behaviorally is represented by a low-voltage fast EEG picture, and is paralleled by poor attention and behavioral efficiency. On the other hand a slightly less activated state, corresponding to alert attentiveness, favors selective and shifting attention, and behavioral efficiency. The optimal alpha rhythm occurs in a relaxed state of wakefulness where attention is not fixed. There are indications that awareness or consciousness shows its broadest sweep or scan and perhaps its lowest threshold in the stage of relaxed wakefulness and optimal alpha rhythm. The threshold is elevated and the field restricted as drowsiness and light sleep develop. It is probably in the stage of light sleep that consciousness is lost, since in that stage there is lack of awareness of things going on externally and lack of ability to make perceptual discriminations. Beyond that point in the direction of deeper sleep there is no awareness or memory for events, except

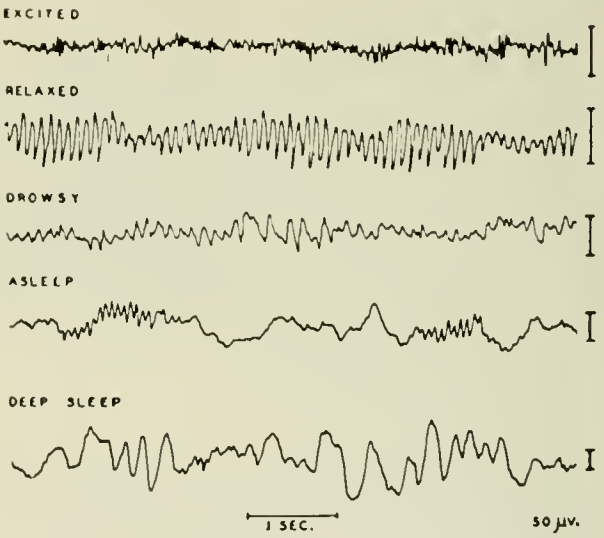



FIG. 11. Normal EEG records characteristic of different stages on the sleep-wakefulness continuum (see table 1). The only major omission in the series would be between *excited* and *relaxed*, where there should be a low-voltage record resembling *excited*, but with less marked activation, labeled *attentive*. [From Jasper (125).]

possibly for dreams which usually are accompanied by a momentary elevation of the pattern of the EEG toward wakefulness and alpha rhythms. There are still many questions about dreams, and recent work on this topic will be taken up subsequently.

With respect to consciousness and attention, shifting upward on the continuum from relaxed wakefulness with alpha waves to alert attentiveness and an activated or desynchronized EEG with low-amplitude fast waves, attention may be heightened or focused

but with definite restrictions upon the span of consciousness. In other words the threshold to slight change in a restricted field of attention may be lowered, but the threshold of awareness for events outside that field may be greatly elevated. This is the role of selective attention for which we sought neurophysiological mechanisms in the functioning of the ARAS and DTPS.

In excited emotion and in situations where strong stimuli are in abundance (sensory overload), there are indications that the ARAS or DTPS may be swamped or blocked so that awareness is either severely restricted or is so broadened as to be useless. Everyday experience attests to the confusion and the unreliability of observations and testimony made under stressful conditions. Higher-voltage fast activity usually characterizes this state in contrast to the lower-amplitude activation pattern of alert attentiveness.

Although sometimes viewed as a kind of epiphenomenon, the EEG representing signs of changing cortical activity seems to mirror changes going on in subcortical mechanisms such as ARAS and DTPS. In some respects and for some purposes this may be more important to know than what one cortical unit among 10 billion may be doing, or how any small sample of units may be responding; yet we need both kinds of information. How does the EEG reflect changes in subcortical mechanisms? We have seen how it changes from wakefulness to sleep and some of these changes we can account for in terms of ARAS and DTPS activity when modified by stimulation, lesions or drugs. Alpha waves may be suppressed by natural sensory stimulation or by stimulation of the reticular formation. In the course of relaxation and quiet alpha waves recede, spindle bursts and slow waves appear, consciousness is lost and sleep pervades. Blocking the ARAS by lesion or barbiturates shifts the EEG pattern from one of activation or alpha waves to one of sleep spindles, slow waves and somnolence. Sleep spindles have been removed in animal preparations by anterior thalamic lesions, a fact suggesting that the transient appearance of sleep spindles during the shift from wakefulness to sleep may represent a shift in the dominance or control manifested by certain thalamic nuclei. Stimulation of medial and intralaminar nuclei of the thalamus by repetitive low-frequency shocks produces recruiting waves in the EEG which resemble the slow waves of sleep, and slightly lower-frequency stimulation actually induces sleep in chronic animal preparations. These are some of the changes reflected in the EEG, and judicious use of it as an indicator will continue to help reveal the effects of even more restricted experimental manipulations of subcortical structures and mechanisms.

As Adrian (5) so well pointed out, we have thought of the cortex as a screen upon which patterns are thrown by different sense organs, but there are even broader problems of attention, perception, recognition and so forth to contend with. The EEG, when further elucidated by analysis of the subcortical mechanisms whose activity it reflects and by microelectrode studies of the substance from which its potentials arise, may well be one of our more important tools in further investigation of higher mental processes.

We still do not know the precise source or origin of the alpha waves, but they are generally believed to be summated dendritic potentials. What determines their time constant and rhythm? Is there a cortical or subcortical pacemaker? We have observed that their time constant is different in young children and adults, but so also is the latency and time constant of evoked potentials, as Ellingson (71) has shown. Are these differences due to structure, chemical constitution, metabolism, maturational changes, lack of development and integration of specific and unspecific sensory mechanisms, or to a combination of factors? How do these characteristics affect the functions subserved? The approaches to these questions must necessarily be broad and must include phylogenetic, ontogenetic and longitudinal approaches as well as the detailed experimental manipulations in acute and chronic animal preparations. In humans, except for limited observations made during operative procedures on the brain, we are mainly limited to external measurements such as the EEG, coupled with psychological and behavioral assessments. By paralleling these with appropriate animal experiments, certain inferences and deductions may be made.

### *EEG and Eye Movement Studies of Dreaming During Sleep*

Loomis *et al.* (169) Blake & Gerard (27) and Blake *et al.* (28) have studied the EEG and general body motility during sleep. Movement of a part of the body or of the whole body during sleep regularly lightens the level of sleep as indicated by the EEG. A movement during the *B* stage of sleep or drowsiness inevitably reinstates a short period of alpha waves, and a major movement during the *D* stage of sleep has frequently been observed to shift the EEG pattern from delta waves to a *C*, *B* or even *A* stage momentarily. Thus it appears that kinesthetic, proprioceptive and tactual stimulation excites the ARAS, and it in

turn changes the EEG in the direction of wakefulness, though usually very briefly.

More recently Aserinsky & Kleitman (13) discovered that periods of rapid conjugate eye movements during sleep were associated with episodes of dreaming. Subsequently Dement and Kleitman (55, 56) combined the EEG and objective measures of eye movements for the study of all-night sleep. They confirmed the fact that rapid eye movements occur periodically during a night of sleep and that if the subject is awakened during or immediately after the series of eye movements, in 80 per cent of the instances he is able to report that he had been dreaming and give the content of the dream. When random awakenings were introduced in the absence of eye movements only 7 per cent reported dreaming and in the majority of these instances the time of awakening fell within 8 min. of the last period of eye movements which suggested that the dream was recalled from the previous eye movement period.

Dement & Wolpert (58) and Dement & Kleitman (57) have greatly extended their observations of eye movements, bodily movement and EEG during sleep, and have determined that there are regular cyclic variations in the depth of sleep as revealed by the EEG and eye movement patterns. Three or four peaks of body and eye movements and sleep lightened to their stage 1 (comparable to *Stage B*) occur during a night. Awakening the sleeper during or immediately after one of these periods elicits a report of dreaming. The dream duration appears to parallel the actual eye movement duration which may last from about 10 to 30 min. Contrary to previous belief, the evidence suggests that long dreams are not experienced in a matter of a few near-waking seconds, but rather that the duration of the dream and the duration of the period of lightened sleep and eye movements tend to correspond. Body movements often seem to terminate the dream sequence. The content analysis of the dreams indicates that eye movements participate in the dream sequence but that body movements do not. External and internal stimuli were found to be unimportant in influencing the course of a dream. The 'dream time' revealed by eye movements appears to correspond with the real or actual time required to experience or participate in the activity revealed by the dream if it were to be relived in real life. The further application of these objective methods of recording eye movements and body movements in association with the EEG, and the correlation of these with the report of the dream upon immediate arousal promises enlightenment about the mechanism of dreams where little existed before.

### *Is Learning During Sleep Possible?*

Simon & Emmons in a critical review entitled 'Learning During Sleep?' (214) raise serious doubt that any of the few published studies, and several unpublished theses, purporting to show that learning can occur during sleep have met the necessary scientific requirements which would justify the conclusion that learning has been induced during sleep. After a critical analysis of the experimental design, statistics, methodology and criteria of sleep employed in these studies, Simon & Emmons conclude that all of them had serious weaknesses in one or more of these areas of criticism. They point out that much of the difficulty in evaluating such studies rests upon a definition of sleep, the establishment of suitable criteria of sleep and, perhaps most important of all, whether the period of sleep training was properly monitored throughout to insure that the criteria of sleep were met.

According to their own apparently carefully controlled experiments, Simon & Emmons (216, 217) report that learning did not occur during actual sleep (comparable to *Stages C* and *D* discussed above). Even when using a less rigid criterion of sleep based on the transition stage from wakefulness to sleep (comparable to *Stage B*), but with the restriction that alpha waves be absent from the record at least 30 sec. before a stimulus and for at least 10 sec. afterward, they still found no significant evidence of learning.

These results would suggest that the best answer that can be given at present to this question is that learning during actual sleep is not possible. Despite this conclusion many commercial enterprises across the country advertise that sleep learning is possible, and offer phonograph records or tape recordings of foreign languages and other difficult-to-learn and time-consuming subjects to be played during the course of a night's sleep or some portion of it.

The important question is whether the user of such a program of sleep learning is being exposed during waking or near-waking states in which case the result if positive would not be sleep learning but conscious or semiconscious waking learning. Even though the sleep-learning program were not turned on until an hour or so after going to bed, we know from the results discussed above in relation to dream periods (56, 58) that there are cycles of oscillation

between deeper sleep and near-waking states throughout the night. In some of the lighter periods (*Stage B*) when alpha rhythms return and eye movements persist for 10 to 30 min. according to Dement & Wolpert (58) there would be considerable opportunity for drowsy, semiconscious or waking learning to occur. Unless the entire period of presumed sleep were monitored by EEG and perhaps eye movement recording as well, there would be no way of knowing whether any accretion of learning which occurred as a result of the night's stimulation was due to learning during periods of actual sleep or of relative wakefulness.

The experiments of Simon & Emmons, though well controlled with respect to sleep and wakefulness by continuous EEG recording, are subject to the criticism that they involved only one night of sleep-learning trials for each subject. It might be argued that a longer period of exposure would be required; however, the nature of their material was such that it might easily have been learned in one night. In one of the experiments 96 items of information pretested before the night of sleep and read with answers at 5-min. intervals during the EEG monitored sleep, were posttested the next morning for recall and recognition. There was no learning of material which had been presented during the *B* to *E* stages as shown by the EEG, performance of the experimental group so exposed being no better than that of a control group given no training. The amount of correct recall increased markedly for those information items presented during periods when alpha waves were present. Since alpha waves when present correlate highly with wakefulness and consciousness, learning during their presence might well be expected. Since they selected their subjects on the basis of their dominant alpha rhythms, the absence of alpha waves for prolonged periods undoubtedly meant deep drowsiness and loss of awareness or light sleep, and as a consequence no significant learning.

What if any are the reasons one might have to expect that learning would be possible during sleep? Let us examine first the implications and conditions of learning during normal wakefulness, then the conditions which exist during sleep which might be presumed to make learning possible or impossible. In normal waking learning the association of two events simultaneously, or successively in reasonable contiguity, one or more times under the proper conditions of psychological set or attention and with the proper motivation, generally results in the development of a bond of relationship between the events which upon the appearance of one tends to recall the other. Repetition strengthens this relationship. In a conditioned reflex situation, a conditioned stimulus is paired with an unconditioned stimulus until through repetition it gains the potential it did not have originally of releasing the response of the unconditioned stimulus. In both of these instances of learning there is implied perceptual discrimination of the stimuli, which requires selective attention, a certain degree of general alertness, and some degree of motivation. Although these and other conditions may be necessary for optimal learning in the waking state, there is no certainty that they would have to obtain during sleep if learning and conditioning were to occur then, since electrical recordings show the cortex, reticular formation, thalamus and hippocampus to be exhibiting very different patterns of activity during sleep than during waking. Since specific sensory pathways remain open during sleep, impulses giving rise to evoked responses still reach specific receiving zones of the cortex, and also reach and affect the thalamus and hippocampus. The reticular formation on the other hand is less responsive and the entire unspecific sensory system including the brain stem, thalamus and cortex has a higher threshold of excitability and exhibits a different pattern of electrical activity.

Sensory messages reaching the cortex do not result in perceptual discrimination in the absence of unspecific influences. The reason for this is not known, nor is it known precisely where perceptual discrimination occurs. As Galambos & Morgan point out in Chapter LXI of this *Handbook* it is not known how or where learning takes place in the brain, although it appears from recent studies that the reticular and limbic systems may have as much to do with this as the cortex. Therefore, on the basis of present neurophysiological knowledge about learning, one cannot prejudge nor preclude the possibility of learning during sleep. However, the burden of proof would seem to reside with those who maintain that it can.

With respect to the lack of consciousness during sleep, and therefore the lack of awareness of and memory for events which occur during sleep, one might wonder how learning could be expected to occur. Lacey *et al.* (150, 151), as well as others have been able to produce what might be called 'unconscious' conditioning. In studying autonomic responses in two groups of college students, they presented a list of words to which association responses were to be given. A shock accompanied 1 of 40 words each time it was presented. For one group that word was one with a rural connotation; for the other, an urban

connotation. Subsequent testing of the words revealed that a conditioned anxiety had spread to words in the list with a rural connotation for the one group and with an urban connotation for the other. Many of the subjects were unaware that they had been shocked on a word belonging to a particular category and that they were responding with autonomic anxiety responses to other words of that category. In this experiment however the subjects were awake and not asleep. They were quite aware of the stimuli as words with meaning, but were 'unconscious' or unaware of the categorization or abstraction process which developed beyond the simple perception of a word. Such extended cognitive conditioning goes on in a brain awake and alert due to shock reinforcement and exists without awareness as a relational process. But what of sleep where the simple perceptual process appears not to develop due to lack of ARAS influence? Can a lower order of perception occur and leave a useful residual in memory? Can dissociation of levels or hierarchies of perception occur during sleep and be redintegrated during subsequent wakefulness?

### *Consciousness, Attention, Hypnosis and the EEG*

CONSCIOUSNESS. The term consciousness has suffered both from the broadness and narrowness of its conception. This is illustrated by a review entitled 'Consciousness Reconsidered' by Schiller (208) and by five volumes covering the annual Macy conferences from 1950–54 entitled *Problems of Consciousness*, edited by Abramson (1). The broad framework of these treatments of consciousness ranges from the anatomical, concerned with the seat or locus of consciousness, to the zoological or phylogenetic approach. Also included are philosophical, psychological, psychoanalytic, anthropological, sociological, biological, biochemical, neurological, neurophysiological and other viewpoints. It is perhaps significant however that the neurophysiological approach because of its recent advances and contributions to new conceptions of brain organization and function has decidedly influenced thinking, and has given new impetus to discussion of an old topic. Here we shall be concerned mainly with certain selected aspects of the neurophysiological, electroencephalographic, psychological and behavioral manifestations of consciousness.

In the Macy conferences and in Schiller's review there is an evident failure to resolve a definition of consciousness which would satisfy the various interdisciplinary approaches to this problem. Because of this the Macy conferences which began with the somewhat restrictive title 'Levels of Consciousness' shortly shifted to *Problems of Consciousness*. In his summary Schiller states: "Exclusively physiological and exclusively introspective accounts are incomprehensive and give rise to artifacts. Although they are complementary, integration of knowledge is hard to achieve because their points of reference and scales of observation are wide apart."

Lindsley (160) has argued for some kind of operational definition of consciousness in terms of which we can observe, measure and evaluate. He proposed that consciousness is a state of awareness, and that underlying this is sensory or perceptual discrimination which might serve as an anchoring point in terms of observation and measurement. Thus to determine the state of awareness of consciousness at some point on the sleep-waking continuum (see table 1) we can measure the intensity and other characteristics of the stimulus necessary to arouse the subject to a point where he can discriminate the stimulus presented. The act of discrimination may be an overt or covert response, the latter being measurable as an autonomic, somatic (electromyographic) or central-nervous-system (electroencephalographic) response, as well as by subjective judgment and verbal report.

Piaget in the 1954 volume of Abramson (1) stated that consciousness might be analyzed in two ways, one, by studying the earliest or most elementary forms of awareness, or by concentrating upon states of consciousness which were in process of disappearing and returning, and two, by studying the developmental changes in awareness as these are revealed by objective criteria of language, judgment and so forth. He discussed the second of these approaches under the heading of consciousness of necessity in which awareness of logical necessity was dealt with as it develops in children. For example, 7-year-olds clearly see the logical necessity of the number of beads in a short broad vial equaling those in a long thin one. This is a cognitive consciousness or a consciousness of relationships, which Piaget attempts to trace developmentally in terms of total operational structures. He believes these structures not only help to explain changes in consciousness, but are eventually isomorphic with corresponding neurological structures. He states that consciousness is essentially a system of meanings that may be cognitive or affective.

We shall now revert to the first approach mentioned by Piaget, namely what are some of the earliest forms of awareness, or when does a newborn infant first manifest signs of awareness. Kleitman in the 1950 and 1954 volumes of Abramson (1) emphasized

the point of view that there is a vertical stratification of consciousness ranging from near zero in the newborn baby asleep (or an adult in deep dreamless sleep) to an alert attentive adult after two cups of coffee. Lindsley in the 1950 volume and Monnier in the 1952 volume also stress the fact that consciousness is a matter of degree and level of complexity of perceptual discrimination. The newborn infant with a relatively nonfunctional cortex or the anencephalic monster without the cortex are rather alike in being essentially brain-stem creatures in whom reflexes and arousal responses exist, but very little differentiation of discrimination and response. Discrimination if present is at its lowest ebb, and attention, except for the crudest form of orienting reflex, is literally absent. As Lindsley (160) has indicated: "Although a newborn or young infant may show reaction to stimulation it is undifferentiated and not at all selective. Sensory discrimination, if present at all, is most elementary, and in this sense one must conceive of consciousness as being very restricted." The onset of the occipital alpha rhythm in the young human infant (see fig. 9) at 3 or 4 months of age appears to be correlated with the first consistent behavioral manifestations of integrated attention. Does the absence of persistent alpha rhythms in sensory zones prior to that indicate a lack of awareness and consciousness in the field of these sense modalities? It probably does so far as perceptual discrimination and integration are concerned. As we observed earlier, the return of alpha waves signifies the emergence from sleep and also the onset of awareness or consciousness of the environment which can only be discriminated as this stage of the EEG develops. There is a correspondence in the development and maturation of the structure and function (EEG) of the brain and the perceptually oriented behavior it manifests.

### *Consciousness and EEG Characteristics*

Let us turn now to the EEG in relation to some reversible changes of consciousness. Gibbs *et al.* (90) were among the early workers to study the EEG changes in epilepsy and conditions of impaired consciousness. Davis & Davis (52) surveyed this topic in a very thorough fashion in 1939, and very little can be added except in respect to interpretation in terms of recent neurophysiological concepts. With regard to determining the state of consciousness and its electrical correlates in the early stages of sleep, they draw upon the description of experiments conducted by Davis *et al.* (53). "The subject lies down to sleep with a rubber bulb in one hand, and is instructed to squeeze it once whenever he feels that he has just 'drifted or floated off' for a moment and twice if he feels that he has awakened from 'real sleep.'. . . The accuracy of the signalling is remarkable, considering how unfavorable drowsiness is for introspection and signalling. . . . The common denominator in the subjective reports of the experience of 'floating' is a depression of *sensory perception.* Some identify the state by suddenly realizing that they have ceased to hear noises or that they have lost their awareness of the bed clothes or the position of their body. Others stress the appearance of visual phantasies or interruptions in the train of logical thought, but in all cases there is loss of awareness, particularly of immediate external stimuli. *This transient clouding of consciousness appears to be correlated with definite objective alterations in the electrical activity of the brain.*" The 'floating or drifting off' experiences occur in the *B* stage when alpha waves are greatly diminished or absent for 5 sec. or more. As these experiences become more persistent and longer lasting, low-voltage delta waves appear and merge into the *C* stage of real sleep with spindle bursts of 14-per-sec. waves.

INDUCED PHYSIOLOGICAL CHANGES. The breathing of an 8 per cent oxygen mixture was carried out in three subjects to the point of unconsciousness by Davis *et al.* (54), with EEG and handwriting as indicators of change of state of consciousness. After 4 min. of low oxygen a subject reported "fullness in the head, ringing in the ears and a desir [*sic*] to breathe more deeply." After 17 min. he felt "fuzzy," dizzy and experienced a spell of remoteness. His writing deteriorated in quality and composition and finally stopped entirely (hand "froze"). In each of the three subjects with the onset of unconsciousness large slow waves became persistent in a 'locked' pattern. Although none realized they had lost consciousness, they were unaware when the mouthpiece of the breathing apparatus had been removed. The slow waves became 'unlocked' after breathing room air for 5 sec. and after 5 sec. more the subject was able to write in a distorted fashion. At this point slow waves were receding. After 2 min. on room air all slow waves had disappeared and the record showed low-voltage fast activity, and not until 4 min. or more did alpha waves and control picture return. Thus we see that the deterioration of consciousness and writing behavior began with the loss of alpha waves, but unconsciousness did not become complete, nor behavior

blocked, until very large slow waves developed a locked pattern. The return of consciousness was correlated with the breaking up of the slow wave pattern, but did not become clear until some alpha waves returned.

Voluntary overbreathing or hyperventilation carried on from 2 to 4 min. will often induce delta waves of increasing magnitude in normal subjects. In 15 experiments the Davises reported consistent results, with modification of consciousness as the high-voltage delta waves became persistent. Subjects failed to respond to commands, although one reported hearing the command and said afterward he was unable to comply. If hyperventilation were carried further, it is quite likely that a complete loss of consciousness would occur.

In connection with Metrazol seizures which had been induced in a schizophrenic patient who had a normal control EEG, it was found that the patient became unconscious when convulsions associated with high-voltage fast waves set in. Lack of consciousness persisted through the subsequent low-voltage, relatively isoelectric period following the cessation of clonic convulsions, and through the high-voltage delta wave period in which waves gradually became better organized and more regular. Consciousness was restored when the electrical activity finally returned to normal frequency ranges. Thus unconsciousness occurred in this instance during high-voltage fast waves, but continued through two or more patterns of slow waves of diverse type. There is always the possibility, however, that unconsciousness which occurs during the fast high-voltage stage in a major seizure shifts into a prolonged period of sleep with slow waves from which the patient eventually arouses. Thus, the slow waves following a convulsion may literally be deep sleep waves which are also accompanied by unconsciousness. But some patients cannot be as readily aroused from such a stage as can a normal person with similar patterns in a stage of deep sleep.

Following coma-producing injections of insulin in a schizophrenic patient, it required better than an hour before all alpha waves disappeared and low-voltage delta waves replaced them. At this point the patient was asleep with obvious loss of consciousness. In about 3 hr. very large 1-to-2-per-sec. slow waves in a locked pattern appeared and continued during the remainder of the coma, which was cleared in 11 min. by an injection of glucose. Forty min. following glucose the EEG was approaching normal and consciousness was restored.

Deep ether and deep alcoholic intoxication both produce large slow delta waves in their unconscious anesthetic and stuporous phases, respectively. Ether initially produces a shift from alpha waves to a fast activity before giving way to delta wave activity of larger and slower nature. Alcohol initially enhances alpha activity, then diminishes and slows it; but no marked changes occur until deep intoxication is reached when the pattern becomes a more or less continuous moderate to high-voltage delta wave activity.

SEIZURE PATTERNS WITH MODIFICATION OF CONSCIOUSNESS. Figure 12 illustrates a spontaneous grand mal or major seizure pattern in a young man 19 years of age. The entire seizure is shown except for the prolonged terminal sleep phase. The attack began with an increase in the voltage of alpha and other activity (at arrow, fig. 12). At the point marked *tonic phase* the patient's limbs and body assumed a rigid extensor position, and his EEG showed a further increase in voltage and amount of fast activity. About 5 sec. after the onset of the tonic phase, when high-voltage fast activity was still marked, consciousness was lost. The tonic phase gradually shifted to a clonic jerking phase, and as this subsided there was a period of flat, isoelectric record which ushered in the complete relaxation of the comatose phase. After some seconds random slow waves began to return and this picture persisted for some time, gradually forming more regular delta waves which eventually disappeared in about 30 min., the EEG returning to near normal.

Figure 13 shows a major seizure induced by electroshock in which essentially the same pattern is exhibited as in the naturally occurring grand mal seizure shown above. Again consciousness was lost at or near the start of the tonic phase. The sequence of tonic extensor phase with high-voltage fast activity, followed by clonic convulsions with slowing of waves to correspond to rate of jerking, isoelectric record corresponding to the relaxed comatose phase, and finally continued relaxation with development of random slow waves, is characteristic of both the induced and natural major attacks. Unconsciousness merges with sleep at the end, and the arousal and preseizure EEG pattern may not return for 15 min. to an hour or more.

In contrast to the major seizures, figure 14 shows a petit mal or minor attack, with characteristic spike and slow wave pattern lasting 12 to 15 sec. with no behavioral change other than opening of the eyes and staring straight ahead. Such an attack usually indicates an 'absence' or momentary 'blank-out,'

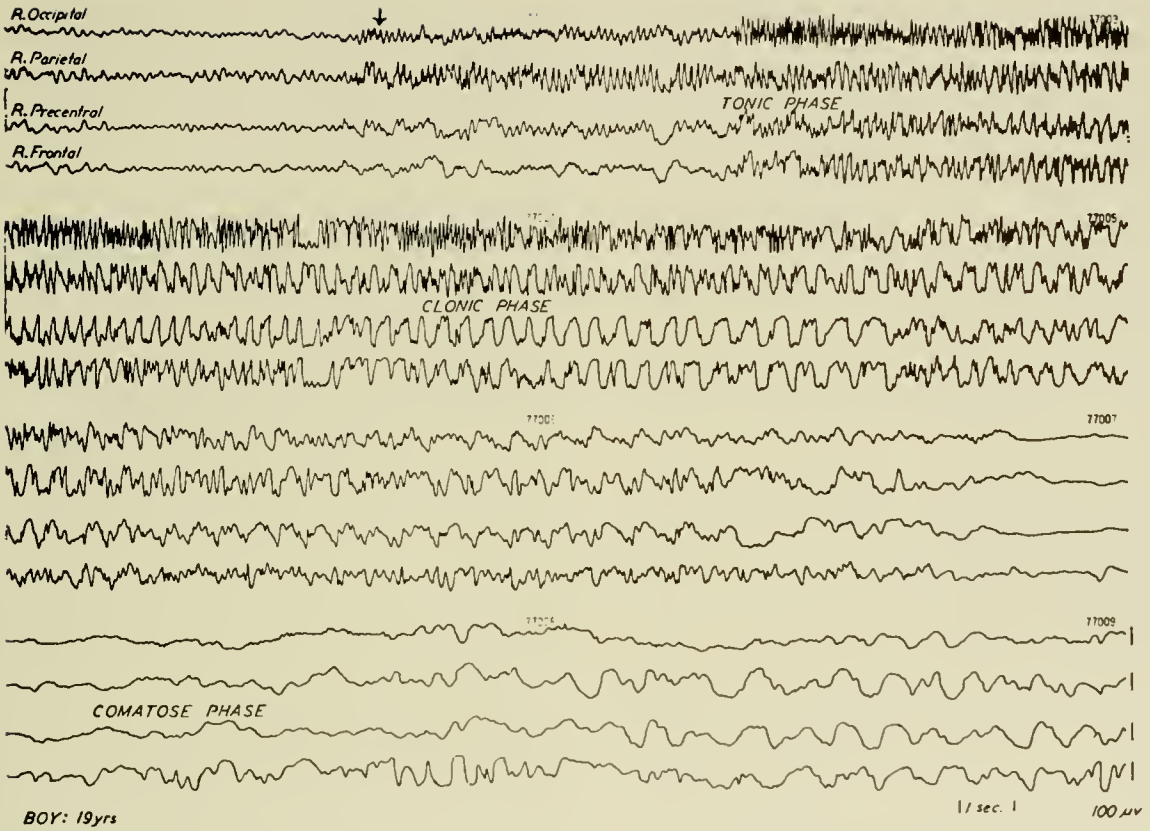



FIG. 12. EEG record of a major grand mal seizure showing the onset with hypersynchrony about 6 sec. before the tonic phase was ushered in with high-voltage fast activity which gradually shifted to slow waves at 3 per sec. and the clonic phase. Consciousness was lost near the onset of the tonic phase during fast high-voltage waves. [From Lindsley, unpublished observations.]

but without falling or necessarily very noticeable change in behavior. If speaking, the patient may stop or continue with poor integration. A movement already started may be fixed or frozen, or may be continued with poor control. Our major concern here is with the state of consciousness and that is variable, ranging from a complete 'blank-out' to partial awareness and ability to continue counting, or to stop counting momentarily and continue again as if nothing had happened. These and other variations to receive, integrate and respond to stimuli and commands are apparently due to the variations in the magnitude and extent of the seizure discharge and perhaps also bear some relationship to its origin, whether in the thalamus, cortex or elsewhere. (See also Chapter XIV by Gastaut & Fischer-Williams in this *Handbook*.)

The loss of consciousness in syncope, and especially carotid sinus syncope, has been attributed to a fall in arterial pressure and decreased oxygen tension of blood in the brain, but Lennox *et al.* (156) and Ferris *et al.* (73) concluded that some other factor than cerebral anoxia must produce unconsciousness in carotid sinus syncope of the central type. Forster *et al.* (76) found unconsciousness associated with slow waves in the circulatory type, but with fast waves in the central type. In recent years Bonvallet *et al.* (29) have brought forth evidence which may have a bearing upon unconsciousness and syncope. They have shown that spontaneous fluctuations of electrocortical activity are related to sympathetic tone, and that visceral and nociceptive stimuli produce marked activation of the cortex and parallel sympathetic changes. Two mechanisms are operating, a direct influx of such stimuli to the bulbar reticular formation with immediate cortical activation, and a delayed humoral process which acts upon the pontomesencephalic reticular activating system and then the cortex. The sympathetic tone may be just as important to the maintenance of wakefulness and consciousness as the influx of proprioceptive and exteroceptive stimuli.

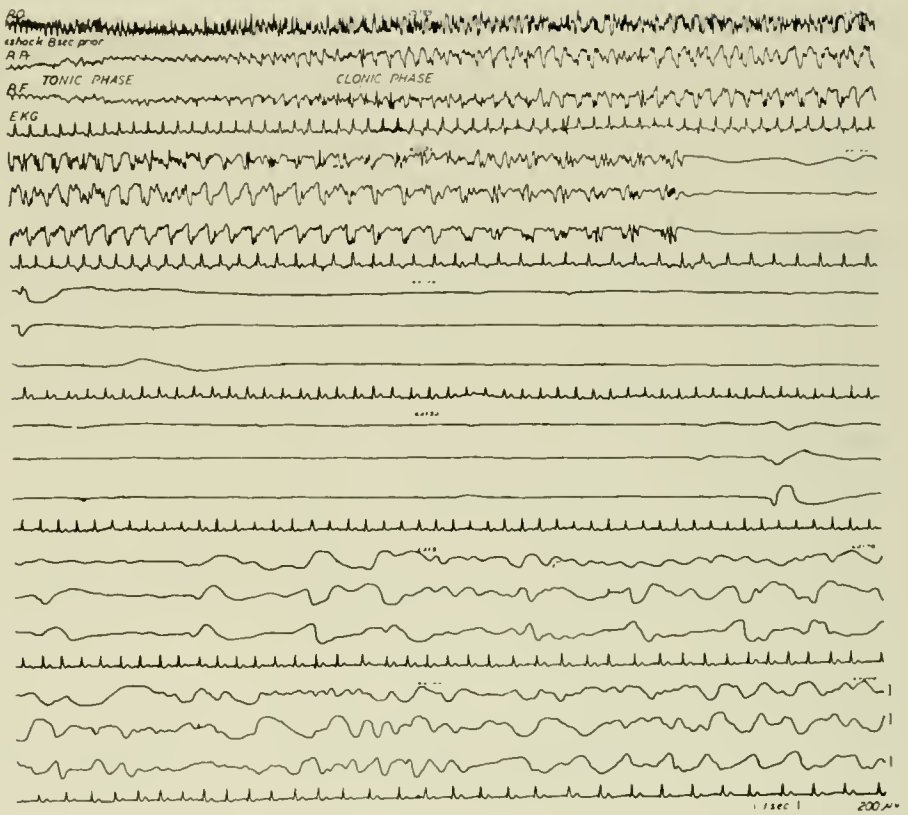



FIG. 13. EEG record of an electroshock convulsion similar to the grand mal attack in fig. 12. The record was started 8 sec. after the shock to avoid shock artifact. The record begins with the tonic phase and high-voltage fast activity; consciousness was lost immediately. The clonic phase follows quickly with first, 3-per-sec. waves, then slowing to 1 per sec., and subsequently to the flat isoelectric period during which the patient was completely relaxed. The end of the record shows large random slow waves gradually organizing into a sequence of large 1-per-sec. waves characteristic of deep sleep. [From Lindsley, unpublished observations.]

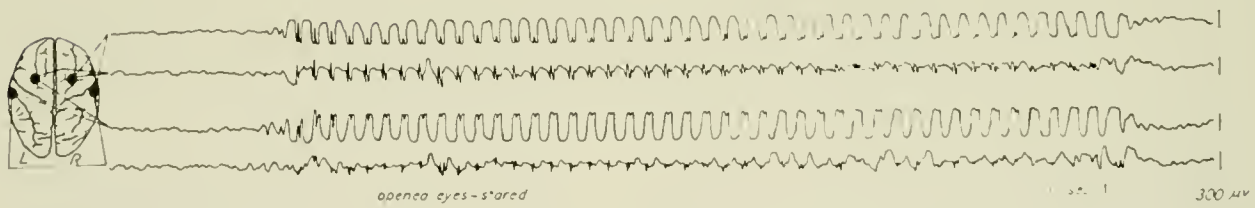



FIG. 14. EEG record of a minor petit mal seizure showing characteristic 'spike-and-slow-wave' sequence. The attack lasted about 14 sec. Consciousness was in abeyance, and there was amnesia for the attack. [From Lindsley, unpublished observations.]

These workers have also demonstrated that distention of the carotid sinus, with experimental control of arterial pressure and cerebral circulation, is capable of inhibiting by nervous transmission the brain-stem activation of the cortex. This is the only known mechanism of afferent influx to the reticular formation which inhibits it, and thus reduces cortical activation and promotes slow-wave development comparable to that in a state of sleep. The influence of sympathetic tone as an activator of the ARAS, or the sudden drop in tone as a deactivator, may under certain emotional or fatigue conditions be able to induce either accentuated hypersynchrony and fast activation waves such as appear to trigger the grand mal attack and produce unconsciousness, or else slow waves which also are frequently associated with unconsciousness. The carotid sinus mechanism and its inhibitory effect on the ARAS may well be a participant in unconsciousness produced in seizures, syncope and narcolepsy.

Gellhorn and collaborators (23, 86, 88) have emphasized the relation of the unspecific to the specific sensory systems in relation to perception, attention and consciousness. Gellhorn (86) feels that interaction of impulses from the diffuse, hypothalamic-cortical projection system with those of the specific projection

systems makes possible the various degrees of awareness that may be distinguished by physiological and psychological criteria. Gellhorn (86) has demonstrated that nociceptive stimuli in lightly anesthetized cats, by interaction with acoustic and optic stimuli, lead to increased reactivity in the projection areas of each of these modalities. A similar interaction between sense modalities has been demonstrated at the reticular formation by Hernández-Peón & Hagbarth (104). These investigators have also shown that afferent and corticifugal influences interact at the reticular formation and result in either interference or facilitation. Both 'occlusion' and 'subliminal fringe' phenomena have been demonstrated. They believe it likely that reticular unresponsiveness, attributable to interaction upon reticular neurons from two or more sources, may well influence sensory perception and consciousness.

Presumably moderate interaction could lead to facilitation, whereas excessive bombardment could result in complete blocking of reticular activation of the cortex causing disturbance in attention and awareness, and even complete loss of consciousness as observed in some seizure states. The kind of sudden and intense barrage from afferent and corticifugal sources in strong emotions could be responsible for the confusion and immobilization often attendant upon such circumstances. The EEG in these conditions (see fig. 11; table 1) usually shows a picture of complete and prolonged flattening or increased high-frequency activity. Such records have been observed in acute and chronic anxiety patients by Cohn (50) and Lindsley (158).

TEMPORAL COURSE OF CONSCIOUSNESS. Fessard (74) has written a very challenging paper on nervous integration and conscious experience. He takes from Cobb (49) the notion: "It is the integration itself, the relationship of one functioning part to another, which is mind and which causes the phenomenon of consciousness." Fessard calls this phenomenon of consciousness an 'experienced integration' or EI. With regard to the temporal organization of consciousness he makes three points: *a*) "each new EI involves a process of reorganization that cannot be instantaneous"; *b*) time and EI are intimately related in that states of consciousness succeed one another; and *c*) in order to know the nature of the integrative processes resulting in EI we must attempt to determine the neural mechanisms corresponding to memory.

In relation to Fessard's first point, it can be shown as in figure 7 that two brief flashes of light 50 msec. apart register as one evoked potential in the visual cortex of the cat, until the reticular formation has been stimulated, and then for a short time afterwards the pair of flashes elicit a pair of evoked potentials. The same two flashes, as Lindsley (162) has found, would be seen by a human subject as one when 50 msec. apart, but as two when 100 msec. separate them. Thus in this instance, as well as in the case of fusion of repetitive flashes above flicker level, successive EI's require time for reorganization and integration. The second point emphasizes Lashley's (155) concept of 'serial order of behavior' and stresses the importance of coherence of temporal sequences, for meaning depends upon order.

Travis (226) has made an attempt to investigate the temporal course of consciousness by recording the EEG from subjects while they were asked to rest and let their minds wander, without attempting to direct the stream of consciousness. Periodically the experimenter said, 'Now,' and the subject reported whatever conscious state was interrupted. A variety of types of imagery was revealed, but mainly visual, auditory and kinesthetic. Reports classified as abstract thinking or mental blankness also were encountered. Alpha blocking or an activation pattern tended to be associated with visual images, kinesthetic sensations and mental effort, while mental blankness and abstract thinking appeared to be accompanied by strong or well-developed alpha waves. Travis concluded that large and regular alpha waves are indicative of a state of cortical equilibrium and represent a generalized psychic activity, whereas the breaking up of this collective action into more rapid and irregular oscillations of much smaller amplitude represents a relatively high degree of specificity in psychic activity. In present-day terms this would be equivalent to saying cortical activation is associated with attention.

Penfield (192–194) has developed an interesting collection of unique observations and subjective reports by the artificial induction of awareness through stimulation of the brain of conscious patients at time of operation. He stresses that sensation cannot be located in the cortex but instead the sensory material is reorganized in a higher center which he identifies as the 'centrencephalon' or 'higher brain stem.' He states that the centrencephalon "must be in certain portions of the diencephalon, mid-brain and pons." Elsewhere (193) he includes "those parts of the higher brain stem, which have symmetrical connections with both hemispheres," pointing out

that the intralaminar systems of the thalamus and the reticular formation of the brain stem and the nonspecific projection systems satisfy the definition. Penfield (194) points out that the "stream of consciousness" as well as "man's experiential record" or memory involves the temporal lobe where direct electrical stimulation in conscious man evokes flashback memories. The hippocampus or a more central portion of the centrencephalic system may be the actual storehouse, but these bear sufficiently close functional relationship to the temporal lobes so that the latter constitute the effective points of activation of such memories and experiences. Penfield (192) adds that not only do sensory impulses arriving at the cortex descend to central integrating centers where "highest level" final integration is presumed to take place but in their final form are impressed upon the premotor cortex for outflow to effectors. However, he believes that there is an alternative pathway for directional voluntary impulses via subcortical motor centers.

Sperry (220) has put forth an interesting point of view indicating that "all brain excitation has ultimately one end, to aid in the regulation of motor coordination. Its patterning throughout is determined on this principle. It follows that efforts to discover the neural correlates of consciousness will be more successful when directed on this basis than when guided by arbitrary correlations with psychic experience, stimulus patterns, or outside reality, or by analogies with various types of thinking machines." He would approach the problem of perception, thinking and even consciousness by attempting to understand motor integration and adjustment. He believes that we have been preoccupied with "sensory avenues to the study of mental processes" and these "will need to be supplemented by increased attention to the motor patterns, and especially to what can be inferred from these regarding the nature of the associative and sensory functions."

ATTENTION AND THE EEG. Jouvet (135) has investigated in man at the time of operation the effect of selective visual attention and the intrusion of distracting stimuli of other modalities upon the surface EEG over the occipital cortex and the subcortical responses in the optic radiations. He has found that repeated single flashes of light produce a marked augmentation of the responses in the optic radiations when the subject was asked to attend to and count the flashes. The surface EEG shows an increase in rapid low-voltage activity at the start of the period of attention and then a decrease. When stimuli of a distracting nature are introduced to other sense modalities than vision, there is a reduction of the subcortical visual responses almost to total disappearance. This would indicate interaction and suppression among the alternative sense modes competing for the field of attention. Olfactory, auditory and nociceptive stimuli were very effective in producing this suppression, but tactile stimulation from objects placed in the hands seemed less effective. Mental calculation and problem solving also caused reductions in the magnitude of the optic radiation responses. In a patient with damage in the brain stem of 6-mo. duration who had in addition to other neurological indications difficulty in maintaining vigilance, it was found that nociceptive stimuli did not affect the visual responses. Jouvet feels that the subcortical reduction of response observed at the time of attention to another sense mode calls for a distinction between the neural mechanisms put in play at the time of the arrest reaction (EEG arousal) and those exhibited at the time of attention. He states that his results confirm those already obtained by others (100, 106) in animals and previously mentioned in this chapter. However, he is uncertain whether the inhibition he has demonstrated is at the level of the lateral geniculate body or the retina, since both have been shown to be affected negatively by reticular stimulation, as well as positively. He did not find habituation of the subcortical visual responses to light flashes presented once a second over a period of several minutes.

Oswald (188) has studied the human EEG under a variety of experimental circumstances relative to vigilance and habituation. During intent listening to brief tones of near-threshold intensity to which the subject was to respond by pressing a key, two tendencies were found, one, for sleep and alertness to alternate regularly and rapidly at the rate of the signals, and two, a slower downward drift toward sleep to the point of failure to respond. The tones were presented at intervals of 10, 5 or 3 sec. during sessions lasting 15 to 30 min. First there was a blocking of alpha to each tone with return for a few seconds between tones. Later this tendency was reversed with alpha blockage appearing between tones and alpha bursts being triggered by the tones. The question arises of course as to whether this is merely a shift from vigilance to a drowsy state, with reversed tendencies for the response, or whether this is a unique reaction of the reticular system to repeated near-threshold stimuli representing a form of habituation. Similar alternations of sleep signs and alertness

appeared while listening to rhythmic music and maintaining apparent wakefulness while tapping to the rhythms. Because of the special interest of the subjects in the music and some tendency to concentrate upon particular instruments or passages, there is possible reason to see in these results the influence of selective attention, with suppression of activity in some periods and not in others, and the alternation or variation of these patterns of attention with sleep-like suppressions of alpha rhythm. It is conceivable also that different areas of the cortex may react differently to selective attention, although this has not been the particular subject of extensive study.

The effect of alerting upon reaction time has been studied by Lansing *et al.* (154). It was found that ordinary visual reaction times to the onset of a visual stimulus without special alerting and when alpha waves were absent or present spontaneously averaged 280 msec. When a brief auditory signal was introduced as a forewarning up to 1 sec. before the visual stimulus, the reaction time was markedly reduced to about 206 msec. if the auditory stimulus preceded the visual stimulus by at least three tenths of a second. Reaction time was reduced if the forewarning stimulus was less than three tenths of a second ahead of the visual stimulus, but much less, and the alpha waves had not been blocked by the time the visual stimulus was presented. In other words unless the interval between the auditory and visual stimuli is great enough, activation or alpha blocking does not occur in time to facilitate the response. Figure 15 shows the curve of reduction of reaction time as a function of the length of the forewarning period and also the curve for the degree of alpha blocking. The two curves show remarkable similarity, suggesting that alpha blocking or activation is indeed related to reduction in reaction time. The set to respond after an alerting signal is presumed to be triggered by the auditory signal acting upon the ARAS, the influence of which is known to be alpha blockade or activation. This process in turn facilitates the speed of processing the over-all reaction. Since input and output time in a visual reaction time situation are relatively constant and fixed, the reduction in reaction time is probably mainly a reduction in central cortical processing time.

A similar type of influence has been demonstrated by Fuster (83) in monkeys trained to make perceptual discriminations between two objects exposed tachistoscopically (see fig. 16). The monkey has been trained to select the correct object in order to get a food reward from under it. After thorough training, he is placed before the one-way screen and can only see

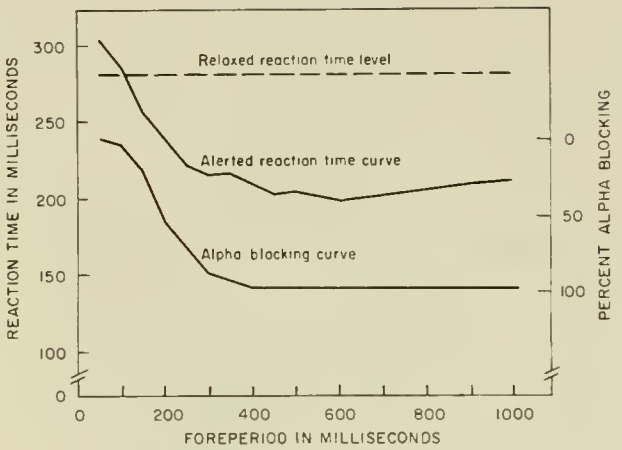



FIG. 15. Reaction time and alpha blocking plotted as a function of the foreperiod interval. Note that the reaction time is reduced to a minimum when the foreperiod ranges from 300 to 1000 msec., and that the *alpha-blocking curve* follows a similar time course. Once activation occurs there is no further reduction of the reaction time. Relaxed unalerted reaction time, 280 msec.; alerted reaction time, minimum 206 msec. [From Lansing *et al.* (154).]

the objects when the tachistoscopic flash of varying durations is presented. As he makes his correct choice, he reaches through a door in front of the object selected which stops the clock and provides an over-all reaction time for the process. The monkey has electrodes implanted in the mesencephalic reticular formation and can be thus stimulated. Figure 17 shows the curves for per cent correct response and reaction time for trials without (control) and with reticular stimulation. It will be noted that reticular stimulation improved performance and reduced reaction time. Here again is an example of facilitation through ARAS influence. Activation or alerting induced in this experiment by direct stimulation of the reticular formation reduced perceptual discrimination reaction time. In the human experiment just cited indirect activation was produced by a forewarning signal and reduced over-all reaction time. In both experiments there is further indication of the facilitation, and thereby a reduction, of central processing time.

EEG IN HYPNOSIS. The question arises, since hypnosis has some characteristics in common with sleep, such as trance-like states with limited awareness, and some in common with selective attention, whether the EEG is one of wakefulness or sleep, and whether any indications of specific arousal or alerting are evident.

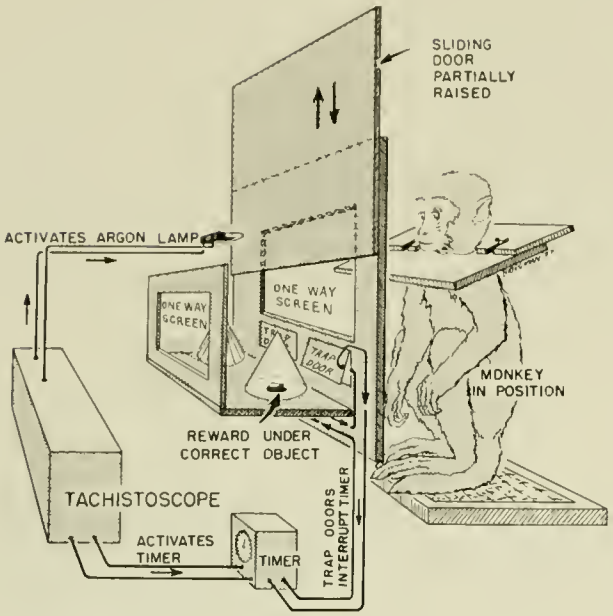



FIG. 16. Visual-discrimination reaction-time apparatus. Monkey is trained to discriminate objects for a reward, then allowed to see the objects only during a brief tachistoscopic flash. The light starts the clock timer; the monkey's choice and reaching through the door stops the clock, so giving the reaction time. [From Fuster (83).]

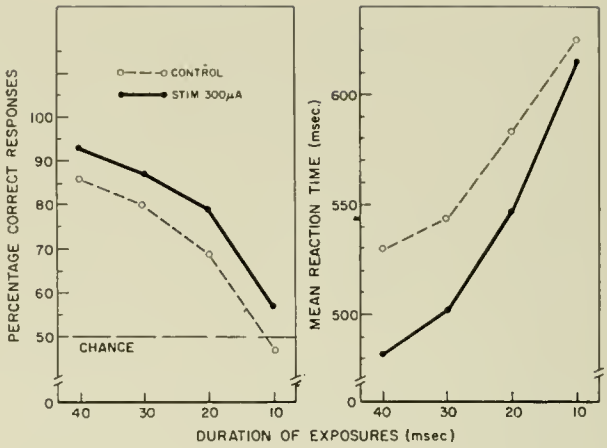



FIG. 17. Percentage of correct response and mean reaction times as a function of tachistoscopic exposure duration. Correct responses increased and reaction times decreased during reticular stimulation (*solid lines*). Each *point* represents 100 trials. [From Fuster (83).]

Although comparatively few studies in the EEG field deal with hypnosis, those that have been published (15, 27, 98, 168, 171, 232) are in general agreement for the most part. In a waking trance, the EEG in hypnosis does not differ significantly from that of the same person in a normal waking state. The EEG does not resemble the EEG in sleep unless a subject in a trance has been allowed to go to sleep or deliberately put to sleep by suggestion. With the general relaxation which occurs during hypnotic episodes, there is sometimes an increase in alpha activity, or a falling off if slight drowsiness supervenes. Unless a special suggestion is made requiring effort or tension, there is no tendency for the EEG to show activation. In general then it can be said that the EEG in hypnosis is similar to that during waking. Under hypnosis the EEG tends to parallel that during normal states and, if the hypnotic subject is required to sleep, he has a sleep EEG; if he is required to solve a problem, his EEG resembles that when he is not under hypnotic influence.

The efficacy of suppressing pain reactions under hypnosis, or of obliterating cognizance to one sense mode in deference to another, suggests a similarity of this aspect of hypnosis to selective attention under normal conditions. Loomis *et al.* (168), however, found that inserting a pin into the arm of a hypnotized subject, after repeated suggestions that he would feel nothing, produced effective alpha blocking lasting 28 sec. Repeated trials produced less effective blocking. The threat to insert the pin into the arm but without actually doing so had no effect on the alpha waves, even when the suggestion was made that the pin was in the arm and painful. They also observed that alpha waves were present during hypnosis as before, and that opening and closing the eyes caused alpha blockade as previously. However, when they suggested that the subject was blind in the presence of light, the alpha waves were not blocked. This result differs from that obtained by others (27, 171, 232), all of whom found that negative suggestion was ineffective in reversing the usual alpha-blocking reaction to light.

Comparatively little progress has been made electroencephalographically or neurophysiologically in coming to grips with the mechanism which might underlie hypnosis and hypnotic phenomena. According to Barber (14) hypnosis is not a "state of consciousness." It is not a "thing" or an "entity." "Hypnosis is a descriptive abstraction referring to an interpersonal relationship which is characterized by a number of overlapping processes." He sees hypnotic phenomena as extensions of normal modes and manners of behaving and reacting, but under the influence of strong "belief" in the hypnotist's influence. Although he strongly emphasizes that hypnosis is not

a state, he recognizes that in normal sleep or awakening from sleep a suggestion is not reacted upon unless the proper 'set' has been established. He finds a similar thing in hypnosis, that a readiness and willingness to respond as the hypnotist directs is a factor in the effectiveness of suggestion. This would seem to imply some kind of plane of reduction, since the subject would not necessarily assume this set under normal conditions. Further careful study is needed of hypnotic influences if the neural mechanism of this remarkable condition is to be understood. Presumably much of this will have to be done with the EEG as the principal liaison between modern neurophysiological conception and the hypothetical states of hypnosis.

SUMMARY

A cursory review of the history of concepts concerning sleep and wakefulness centers in the brain has been attempted with impressions of the steps which have led to the modern concept of wakefulness as dependent upon the reticular system. Several sources of stimulation which influence the reticular formation in the lower brain stem and, through it, the ascending reticular activating system (ARAS) are discussed. The ARAS influences the cerebral cortex and higher brain centers diffusely, but may also have more differentiated effects, some of which may act through the diffuse thalamic projection system (DTPS) in such a manner as to regulate cortical activity and excitability, especially in associational fields. In addition to this nonspecific influence the ARAS and DTPS may act differentially with respect to the fields of reception served by the specific thalamic projection systems (STPS).

Wakefulness is maintained by excitation of the reticular formation and the ARAS through collaterals from all sensory pathways, by corticifugal impulses originating in various regions of the cortex and by humoral factors which affect particularly the rostral portions of the reticular formation. Increased activity in the ARAS through any of these sources of excitation acts upon the cortex by changing the pattern of its electrical activity from the slow waves and spindle bursts of sleep, or the alpha waves of relaxed wakefulness, to a pattern of low-voltage fast waves, commonly referred to as 'activation.' Electrocortical activation is accompanied by behavioral arousal and by alertness and attention.

The elusive term 'consciousness' has been considered as a graded form of awareness, ranging from the simplest perceptual discriminations to the more complex cognitive forms of abstraction and thinking. It has no precise locus on the sleep-wakefulness continuum described in terms of EEG patterns, behavioral characteristics and states of awareness. Unconsciousness in which perceptual contact with the environment is lost can be identified roughly with the onset of sleep in *Stage C* of the EEG in which delta waves and 14-per-sec. spindle bursts predominate. Other forms of unconsciousness induced by breathing low oxygen mixtures, by hyperventilation, by insulin coma, by deep alcoholic intoxication and by some seizure states are mainly associated with the onset and persistence of large and slow waves. In grand mal seizures and in some physiological, drug and anesthetic conditions, loss of consciousness is associated with high-voltage fast activity.

Attention is closely allied to arousal and wakefulness and, like wakefulness and consciousness, appears to be a graded phenomenon extending from general alerting, as in the orienting reflex, to specific alerting, as when attention is focused upon a given sense mode and dominates sensory input to the point of exclusion of other sense modes. Still higher or more finely focused attention may be restricted to a limited aspect of a given sense mode.

Recent neurophysiological findings have been considered which not only broaden the scope of modern concepts of brain organization and function, but bear specifically upon the mechanisms which may underlie and subserve the processes of attention, perception and learning.

REFERENCES

1. Abramson, H. A. (editor). *Problems of Consciousness.* New York: Macy, 1950–54.
2. Adey, W. R., J. P. Segundo and R. B. Livingston. *J. Neurophysiol.* 20: 1, 1957.
3. Adey, W. R., S. Sunderland and C. W. Dunlop. *Electroencephalog. & Clin. Neurophysiol.* 9: 309, 1957.
4. Adrian, E. D. *J. Physiol.* 88: 127, 1936.
5. Adrian, E. D. *The Physical Background of Perception.* Oxford: Clarendon Press, 1947.
6. Adrian, E. D. and B. H. C. Matthews. *Brain* 57: 355, 1934.
7. Akimoto, H. and O. Creutzfeldt. *Arch. Psychiat.* 196: 494, 1957.
8. Akimoto, H., N. Yamaguchi, K. Okabe, T. Nakagawa, K. Abe, H. Torii and K. Masahashi. *Folia psychiat. neurol. Japonica* 10: 117, 1956.
9. Albe-Fessard, D., C. Rocha-Miranda and E. Oswaldo-Cruz. *Electroencephalog. & Clin. Neurophysiol.* 11: 777, 1959.
10. Albe-Fessard, D. and A. Rogeul. *Electroencephalog. & Clin. Neurophysiol.* 10: 131, 1958.

11. Amassian, V. E. and R. DeVito. *J. Neurophysiol.* 17: 575, 1954.
12. Amassian, V. E. and H. H. Waller. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Procter, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 69.
13. Aserinsky, E. and N. Kleitman. *J. Appl. Physiol.* 8: 1, 1955.
14. Barber, T. X. *J. Psychol.* 45: 115, 1958.
15. Barker, W. and S. Burgwin. *A.M.A. Arch. Neurol. Psychiat.* 62: 412, 1949.
16. Bartley, S. H. and G. H. Bishop. *Am. J. Physiol.* 103: 173, 1933.
17. Bartley, S. H. and G. H. Bishop. *Am. J. Physiol.* 103: 159, 1933.
18. Beattie, J. and D. Sheehan. *J. Physiol.* 81: 218, 1934.
19. Berger, H. *Arch. Psychiat.* 87: 527, 1929.
20. Berger, H. *J. Psychol. u. Neurol.* 40: 160, 1930.
21. Berger, H. *Arch. Psychiat.* 94: 16, 1931.
22. Berger, H. *Arch. Psychiat.* 97: 6, 1932.
23. Bernhaut, M., E. Gellhorn and A. T. Rasmussen. *J. Neurophysiol.* 16: 21, 1953.
24. Bishop, G. H. *Am. J. Physiol.* 103: 213, 1933.
25. Bishop, G. H. *Cold Spring Harbor Symp. Quant. Biol.* 4: 305, 1936.
26. Bishop, G. H. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 413.
27. Blake, H. and R. W. Gerard. *Am. J. Physiol.* 119: 692, 1937.
28. Blake, H., R. W. Gerard and N. Kleitman. *J. Neurophysiol.* 2: 48, 1939.
29. Bonvallet, M., P. Dell and G. Hiebel. *Electroencephalog. & Clin. Neurophysiol.* 6: 119, 1954.
30. Bradley, P. B. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 123.
31. Bradley, P. B. and J. Elkes. *J. Physiol.* 120: 14P, 1953.
32. Bradley, P. B. and J. Elkes. *Brain* 80: 77, 1957.
33. Bremer, F. *Compt. rend. Soc. de biol.* 118: 1235, 1935.
34. Bremer, F. *Compt. rend. Soc. de biol.* 122: 460, 1936.
35. Bremer, F. *Compt. rend. Soc. de biol.* 122: 464, 1936.
36. Bremer, F. and N. Stoupel. *Acta neurol. et psychiat. belg.* 58: 401, 1958.
37. Bremer, F. and N. Stoupel. *Arch. internat. physiol.* 67: 240, 1959.
38. Bremer, F. and C. Terzuolo. *Arch. internat. Physiol.* 62: 157, 1954.
39. Brierley, J. B. and L. Beck. In: *Neurological Basis of Behaviour*, edited by G. E. W. Wolstenholme and C. M. O'Connor. Boston: Little, 1958, p. 90.
40. Brodal, A. *The Reticular Formation of the Brain Stem: Anatomical Aspects and Functional Correlations.* Edinburgh: Oliver, 1957.
41. Buser, P. and P. Borenstein. *Electroencephalog. & Clin. Neurophysiol.* 11: 285, 1959.
42. Buser, P., P. Borenstein and J. Bruner. *Electroencephalog. & Clin. Neurophysiol.* 11: 305, 1959.
43. Buser, P., M. Jouvet and R. Hernández-Peón. *Acta neurol. latinoam.* 4: 268, 1958.
44. Chang, H.-T. *J. Neurophysiol.* 13: 235, 1950.
45. Chang, H.-T. *J. Neurophysiol.* 14: 95, 1951.
46. Chang, H.-T. *J. Neurophysiol.* 15: 5, 1952.
47. Chow, K. L. *A.M.A. Arch. Neurol. & Psychiat.* 71: 762, 1954.
48. Chow, K. L., W. C. Dement and S. A. Mitchell, Jr. *Electroencephalog. & Clin. Neurophysiol.* 11: 107, 1959.
49. Cobb, S. *A.M.A. Arch. Neurol. & Psychiat.* 67: 172, 1952.
50. Cohn, R. *J. Nerv. & Ment. Dis.* 104: 351, 1946.
51. Creutzfeldt, O., G. Baumgartner and R. Jung. *Electroencephalog. & Clin. Neurophysiol.* 8: 163, 1956.
52. Davis, H. and P. A. Davis. *A. Res. Nerv. & Ment. Dis., Proc.* 19: 50, 1939.
53. Davis, H., P. A. Davis, A. L. Loomis, E. N. Harvey and G. Hobart. *J. Neurophysiol.* 1: 24, 1938.
54. Davis, P. A., H. Davis and J. W. Thompson. *Am. J. Physiol.* 123: 51, 1938.
55. Dement, W. *J. Nerv. & Ment. Dis.* 122: 263, 1955.
56. Dement, W. and N. Kleitman. *J. Exper. Psychol.* 53: 339, 1957.
57. Dement, W. and N. Kleitman. *Electroencephalog. & Clin. Neurophysiol.* 9: 673, 1957.
58. Dement, W. and E. A. Wolpert. *J. Exper. Psychol.* 55: 543, 1958.
59. Dempsey, E. W. and R. S. Morison. *Am. J. Physiol.* 135: 293, 1942.
60. Dempsey, E. W. and R. S. Morison. *Am. J. Physiol.* 135: 301, 1942.
61. Dempsey, E. W. and R. S. Morison. *Am. J. Physiol.* 138: 238, 1943.
62. Derbyshire, A. J., B. Rempel, A. Forbes and E. F. Lambert. *Am. J. Physiol.* 116: 577, 1936.
63. Desmedt, J. E. and K. Mechelse. *Proc. Soc. Exper. Biol. & Med.* 99: 772, 1958.
64. Doty, R. W., E. C. Beck and K. A. Kool. *Exper. Neurol.* 1: 360, 1959.
65. Droogleever-Fortuyn, J. *Electroencephalog. & Clin. Neurophysiol.* Suppl. 4: 149, 1953.
66. Dumont, S. and P. Dell. *J. physiol., Paris* 50: 261, 1958.
67. Dusser de Barenne, J. G. and W. S. McCulloch. *J. Neurophysiol.* 1: 176, 1938.
68. Ebbecke, U. In: *Handbuch der normalen und pathologischen Physiologie*, edited by A. Bethe, G. von Bergmann, G. Embden and A. Ellinger. Berlin: Springer, 1926, vol. 17, p. 563.
69. Eidelberg, E., W. Hyman and J. D. French. *Acta neurol. latinoam.* 4: 279, 1958.
70. Elkes, J. In: *Neurological Basis of Behaviour*, edited by G. E. W. Wolstenholme and C. M. O'Connor. Boston: Little, 1958, p. 303.
71. Ellingson, R. J. *Electroencephalog. & Clin. Neurophysiol.* 10: 31, 1958.
72. Erulkar, S. D., J. E. Rose and P. W. Davies. *Bull. Johns Hopkins Hosp.* 99: 55, 1956.
73. Ferris, E. B., Jr., R. B. Capps and S. Weiss. *Medicine* 14: 377, 1935.
74. Fessard, A. E. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer, H. H. Jasper and J. F. Delafresnaye. Oxford: Blackwell, 1954, p. 200.
75. Forbes, A. and B. R. Morison. *J. Neurophysiol.* 2: 112, 1939.
76. Forster, F. M., E. Roseman and F. A. Gibbs. *A.M.A. Arch. Neurol. & Psychiat.* 48: 957, 1942.
77. French, J. D., R. Hernández-Peón and R. B. Livingston. *J. Neurophysiol.* 18: 74, 1955.

78. French, J. D. and H. W. Magoun. *A.M.A. Arch. Neurol. & Psychiat.* 68: 591, 1952.
79. French, J. D., M. Verzeano and H. W. Magoun. *A.M.A. Arch. Neurol. & Psychiat.* 69: 505, 1953.
80. French, J. D., F. K. von Amerongen and H. W. Magoun. *A.M.A. Arch. Neurol. & Psychiat.* 68: 577, 1952.
81. Freudenberg, R. K., P. Glees, S. Obrador, B. Foss and M. Williams. *J. Ment. Sc.* 96: 143, 1950.
82. Funderburk, W. H. and T. J. Case. *Electroencephalog. & Clin. Neurophysiol.* 3: 213, 1951.
83. Fuster, J. M. *Science* 127: 150, 1958.
84. Galambos, R. *J. Neurophysiol.* 19: 424, 1956.
85. Galambos, R., G. Sheatz and V. G. Vernier. *Science* 123: 376, 1956.
86. Gellhorn, E. *Arch ges. Physiol.* 255: 75, 1952.
87. Gellhorn, E. *Autonomic Imbalance and the Hypothalamus.* Minneapolis: Univ. Minnesota Press, 1957.
88. Gellhorn, E., W. P. Koella and H. M. Ballin. *J. Neurophysiol.* 17: 14, 1954.
89. Gernandt, B. E. and C.-A. Thulin. *J. Neurophysiol.* 18: 113, 1955.
90. Gibbs, F. A., H. Davis and W. G. Lennox. *A.M.A. Arch. Neurol. & Psychiat.* 34: 1113, 1935.
91. Gillespie, R. D. *Sleep and the Treatment of its Disorders.* London: Baillière, Tindall & Cox, 1929.
92. Granit, R. J. and B. R. Kaada. *Acta physiol. scandinav.* 27: 130, 1952.
93. Haenel, H. *Med. Klin. (Munich)* 21: 1258, 1925.
94. Hagbarth, K.-E. and D. I. B. Kerr. *J. Neurophysiol.* 17: 295, 1954.
95. Hanbery, J. W., C. Ajmone-Marsan and M. Dilworth. *Electroencephalog. & Clin. Neurophysiol.* 6: 103, 1954.
96. Hanbery, J. and H. H. Jasper. *J. Neurophysiol.* 16: 252, 1953.
97. Head, H. and G. Holmes. *Brain* 34: 102, 1911.
98. Heiman, H. and T. Spoerri. *Monatsschr. Psychiat. u. Neurol.* 125: 261, 1953.
99. Henry, C. E. *J. Exper. Psychol.* 29: 117, 1941.
100. Hernández-Peón, R. *Acta neurol. latinoam.* 1: 256, 1955.
101. Hernández-Peón, R., H. Brust-Carmona, E. Eckhaus, E. Lopez-Mendoza and C. Alcocer-Cuaron. *Acta neurol. latinoam.* 4. 111, 1958.
102. Hernández-Peón, R., C. Guzman-Flores, M. Alcaraz and A. Fernandez-Guardiola. *Acta neurol. latinoam.* 3: 1, 1957.
103. Hernández-Peón, R., C. Guzman-Flores, M. Alcaraz and A. Fernandez-Guardiola. *Acta neurol. latinoam.* 4: 121, 1958.
104. Hernández-Peón, R. and K.-E. Hagbarth. *J. Neurophysiol.* 18: 44, 1955.
105. Hernández-Peón, R., M. Jouvet and H. Scherrer. *Acta neurol. latinoam.* 3: 144, 1957.
106. Hernández-Peón, R., H. Scherrer and M. Jouvet. *Science* 123: 331, 1956.
107. Hernández-Peón, R., H. Scherrer and M Velasco. *Acta neurol. latinoam.* 2: 8, 1956.
108. Herrick, C. J. and G. H. Bishop. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 353.
109. Hess, R., K. Akert and W. P. Koella. *Rev. neurol.* 83: 537, 1950.
110. Hess, R., W. P. Koella and K. Akert. *Electroencephalog. & Clin. Neurophysiol.* 5: 75, 1953.
111. Hess, W. R. *Arch. Psychiat.* 86: 287, 1929.
112. Hess, W. R. *Arch. Psychiat.* 88: 813, 1929.
113. Hess, W. R. *Compt. rend. Soc. de biol.* 107: 1333, 1931.
114. Hess, W. R. *Helvet. physiol. et pharmacol. acta* 2: 137, 1944.
115. Hess, W. R. *Helvet. physiol. et pharmacol. acta* 2: 305, 1944.
116. Hess, W. R. *Das Zwischenhirn: Syndrom, Lakalisationen, Funktionen.* Basel: Schwabe, 1949.
117. Hess, W. R. *J. physiol., Paris* 41: 61-A, 1949.
118. Hess, W. R. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer, H. H. Jasper and J. F. Delafresnaye. Oxford: Blackwell, 1954, p. 117.
119. Hubel, D. H., C. O. Henson, A. Rupert and R. Galambos. *Science* 129: 1279, 1959.
120. Hugelin, A., M. Bonvallet and P. Dell. *Rev. neurol.* 89: 419, 1953.
121. Hughes, J. G., B. Ehemann and U. A. Brown. *Am. J. Dis. Child.* 76: 503, 1948.
122. Hughes, J. G., B. Ehemann and F. S. Hill. *Am. J. Dis. Child.* 77: 310, 1949.
123. Ingram, W. R. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 535.
124. Jarcho, L. W. *J. Neurophysiol.* 12: 447, 1949.
125. Jasper, H. H. In: *Epilepsy and Cerebral Localization*, edited by W. Penfield and T. C. Erickson. Springfield: Thomas, 1941.
126. Jasper, H. H. *Electroencephalog. & Clin. Neurophysiol.* 1: 405, 1949.
127. Jasper, H. H. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer, H. H. Jasper and J. F. Delafresnaye. Oxford: Blackwell, 1954, p. 374.
128. Jasper, H. H. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 319.
129. Jasper, H. H. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 37.
130. Jasper, H. H. and C. Ajmone-Marsan. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 493, 1952.
131. Jasper, H. H., C. Ajmone-Marsan and J. Stoll. *A.M.A. Arch. Neurol. & Psychiat.* 67: 155, 1952.
132. Jasper, H. H. and J. Droogleever-Fortuyn. *A. Res. Nerv. & Ment. Dis., Proc.* 26: 272, 1947.
133. Jasper, H. H., R. Naquet and E. E. King. *Electroencephalog. & Clin. Neurophysiol.* 7: 99, 1955.
134. Jasper, H., G. F. Ricci and B. Doane. In: *Neurological Basis of Behaviour*, edited by G. E. W. Wolstenholme and C. M. O'Connor. Boston: Little, 1958, p. 277.
135. Jouvet, M. *Rev. Psychol. Francaise* 2, No. 4: 1, 1957.
136. Jouvet, M. and R. Hernández-Peón. *Electroencephalog. & Clin. Neurophysiol.* Suppl. 6: 39, 1956.
137. Jung, R., O. Creutzfeldt and O.-J. Grüsser. *Deutsche med. Wchnschr.* 82: 1050, 1957. (English translation: *German M. Month.* 3: 1, 1958.)
138. Kabat, H., H. W. Magoun and S. W. Ranson. *J. Comp. Neurol.* 63: 211, 1936.
139. Karplus, J. P. and A. Kreidl. *Arch. ges. Physiol.* 129: 138, 1909.
140. Kayser, C. *J. physiol., Paris* 41: 1-A, 1949.

141. Kerr, D. I. B and K.-E. Hagbarth. *J. Neurophysiol.* 18: 362, 1955.
142. Kerr, F. W. L. and H. L. O'Leary. *Electroencephalog. & Clin. Neurophysiol.* 9: 461, 1957.
143. Killam, K. F. and E. K. Killam. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 111.
144. Klaue, R. *J. Psychol. u. Neurol.* 47: 510, 1937.
145. Kleitman, N. *Sleep and Wakefulness*. Chicago: Univ. Chicago Press, 1939.
146. Kleitman, N. and N. Camille. *Am. J. Physiol.* 100: 474, 1932.
147. Knott, J. R., F. A. Gibbs and C. E. Henry. *J. Exper. Psychol.* 31: 465, 1942.
148. Knott, J. R., C. E. Henry and J. M. Hadley. *J. Exper. Psychol.* 24: 157, 1939.
149. Kovacs, L. *Gior psichiat. e neuropat.* 60: 344, 1932.
150. Lacey, J. I. and R. L. Smith. *Science* 120: 1045, 1954.
151. Lacey, J. I., R. L. Smith and A. Green. *Psychosom. Med.* 17: 208, 1955.
152. Landis, C. and W. A. Hunt. *The Startle Pattern*. New York: Farrar & Rinehart, 1939.
153. Lansing, R. W. *Electroencephalog. & Clin. Neurophysiol.* 9: 497, 1957.
154. Lansing, R. W., E. Schwartz and D. B. Lindsley. *J. Exper. Psychol.* 58: 1, 1959.
155. Lashley, K. S. In: *Cerebral Mechanisms in Behavior*, edited by L. Jeffress. New York: Wiley, 1951, p. 112.
156. Lennox, W. G., F. A. Gibbs and E. L. Gibbs. *A.M.A. Arch. Neurol. & Psychiat.* 34: 1001, 1935.
157. Li, C.-L., C. Cullen and H. H. Jasper. *J. Neurophysiol.* 19: 131, 1956.
158. Lindsley, D. B. In: *Second International Symposium on Feelings and Emotions*, edited by M. L. Reymert. New York: McGraw-Hill, 1950, p. 238.
159. Lindsley, D. B. *Electroencephalog. & Clin. Neurophysiol.* 4: 443, 1952.
160. Lindsley, D. B. In: *Clinical Neurosurgery*, edited by I. J. Jackson and R. K. Thompson. Baltimore: Williams & Wilkins, 1957, p. 175.
161. Lindsley, D. B. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 513.
162. Lindsley, D. B. In: *Description and Analysis of Behavior*, edited by R. Patton. Pittsburgh: Univ. Pittsburgh Press, 1958, p. 48.
163. Lindsley, D. B., J. Bowden and H. W. Magoun. *Electroencephalog. & Clin. Neurophysiol.* 1: 475, 1949.
164. Lindsley, D. B., L. H. Schreiner, W. B. Knowles and H. W. Magoun. *Electroencephalog. & Clin. Neurophysiol.* 2: 483, 1950.
165. Lindsley, D. B., L. H. Schreiner and H. W. Magoun. *J. Neurophysiol.* 12: 197, 1949.
166. Loomis, A. L., E. N. Harvey and G. Hobart. *Science* 81: 239, 1935.
167. Loomis, A. L., E. N. Harvey and G. Hobart. *Science* 82: 198, 1935.
168. Loomis, A. L., E. N. Harvey and G. Hobart. *J. Exper. Psychol.* 19: 249, 1936.
169. Loomis, A. L., E. N. Harvey and G. Hobart. *J. Exper. Psychol.* 21: 127, 1937.
170. Loomis, A. L., E. N. Harvey and G. A. Hobart. *J. Neurophysiol.* 1: 413, 1939.
171. Lundholm, H. and H. Löwenbach. *Character & Personality* 11: 145, 1942.
172. Magoun, H. W. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 480, 1952.
173. Magoun, H. W. and R. Rhines. *J. Neurophysiol.* 9: 165, 1946.
174. Marinesco, G., O. Sager and A. Kreindler. *Ztschr. ges. Neurol. Psychiat.* 122: 23, 1929.
175. Mauthner, L. *Wein. med. Wchnschr.* 40: 962, 1001, 1049, 1890.
176. Monnier, M., M. Kalberer and P. Krupp. XXI Internat. Physiol. Congress, Buenos Aires, 1959.
177. Monnier, M. and R. Tissot. In: *Neurological Basis of Behaviour*, edited by G. E. W. Wolstenholme and C. M. O'Connor. Boston: Little, 1958, p. 105.
178. Morgan, C. T. and E. Stellar. *Physiological Psychology*. New York: McGraw-Hill, 1950, p. 357.
179. Morison, R. S. and E. W. Dempsey. *Am. J. Physiol.* 135: 281, 1942.
180. Morison, R. S. and E. W. Dempsey. *Am. J. Physiol.* 138: 297, 1942.
181. Moruzzi, G. and H. W. Magoun. *Electroencephalog. & Clin. Neurophysiol.* 1: 455, 1949.
182. Nauta, W. J. H. *J. Neurophysiol.* 9: 285, 1946.
183. Nauta, W. J. H. and D. G. Whitlock. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer, H. H. Jasper and J. F. Delafresnaye. Oxford: Blackwell, 1954, p. 81.
184. Nekhorocheff, I. *Rev. neurol.* 82: 487, 1950.
185. Niemer, W. T. and J. Jimenez-Castelanos. *J. Comp. Neurol.* 93: 101, 1950.
186. O'Leary, J. L. and L. A. Coben. *Physiol. Rev.* 38: 243, 1958.
187. Olszewski, J. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer, H. H. Jasper and J. F. Delafresnaye. Oxford: Blackwell, 1954, p. 54.
188. Oswald, I. *J. Ment. Sc.* 105: 269, 1959.
189. Pavlov, I. *Scient. Month.* 17: 603, 1923.
190. Pavlov, I. *Conditioned Reflexes*. New York: Oxford, 1927.
191. Pechtel, C., J. H. Masserman, L. Schreiner and M. Levitt. *J. Nerv. & Ment. Dis.* 121: 26, 1955.
192. Penfield, W. *Brain* 77: 1, 1954.
193. Penfield, W. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer, H. H. Jasper and J. F. Delafresnaye. Oxford: Blackwell, 1954, p. 284.
194. Penfield, W. *XIV Internat. Congr. Psychol., Proc.* 47, 1955.
195. Pieron, H. *Le problème physiologique du sommeil*. Paris: Masson, 1913.
196. Ploog, D. *Fortschr. Neurol., Psychiat.* 21: 16, 1953.
197. Purpura, D. P. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 435.
198. Ramón y Cajal, S. *Trab. Lab. Invest. Biol. Univ. Madrid* 2: 5, 1903.
199. Ranson, S. W., H. Kabat and H. W. Magoun. *A.M.A. Arch. Neurol. & Psychiat.* 33: 467, 1934.
200. Ranson, S. W. and H. W. Magoun. *Ergeb. Physiol. biol. Chem. u. exptl. Pharmakol.* 41: 56, 1939.
201. Rose, J. E. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 454, 1952.

202. Rosenblueth, A. and W. B. Cannon. *Am. J. Physiol.* 135: 690, 1942.
203. Rossi, G. F. and A. Brodal. *A. M. A. Arch. Neurol. & Psychiat.* 78: 439, 1957.
204. Rossi, G. F. and A. Zanchetti. *Arch. ital. biol.* 95: 199, 1957.
205. Rothballer, A. B. *Electroencephalog. & Clin. Neurophysiol.* 8: 603, 1956.
206. Scheibel, M. E. and A. B. Scheibel. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 31.
207. Scheibel, M., A. Scheibel, A. Mollica and G. Moruzzi. *J. Neurophysiol.* 18: 309, 1955.
208. Schiller, F. *A.M.A. Arch. Neurol. & Psychiat.* 67: 199, 1952.
209. Schreiner, L. H., D. B. Lindsley and H. W. Magoun. *J. Neurophysiol.* 12: 207, 1949.
210. Schreiner, L. H., D. M. Rioch, C. Pechtel and J. H. Masserman. *J. Neurophysiol.* 16: 234, 1953.
211. Segundo, J. P. *Acta neurol. latinoam.* 3: 245, 1957.
212. Segundo, J. P., R. Arana and J. D. French. *J. Neurosurg.* 12: 601, 1955.
213. Sharpless, S. and H. Jasper. *Brain* 79: 655, 1956.
214. Simon, C. W. and W. H. Emmons. *Psychol. Bull.* 52: 328, 1955.
215. Simon, C. W. and W. H. Emmons. *Science* 124: 1066, 1956.
216. Simon, C. W. and W. H. Emmons. *J. Exper. Psychol.* 51: 89, 1956.
217. Simon, C. W. and W. H. Emmons. *Am. J. Psychol.* 69: 76, 1956.
218. Smith, J. R. *J. genet. Psychol.* 53: 471, 1938.
219. Speigel, E. A. *Ztschr. ges. exper. Med.* 55: 183, 1927.
220. Sperry, R. W. *Am. Scientist* 40: 291, 1952.
221. Sprague, J. M., L. H. Schreiner, D. B. Lindsley and H. W. Magoun. *J. Neurophysiol.* 11: 501, 1948.
222. Starzl, T. E. and H. W. Magoun. *J. Neurophysiol.* 14: 133, 1951.
223. Starzl, T. E. and D. G. Whitlock. *J. Neurophysiol.* 15: 449, 1952.
224. Taussig, L. *Rev. neurol. Psychiat., Prague* 28: 387, 1931.
225. Tissot, R. and M. Monnier. *Helvet. physiol. et pharmacol. Acta* 16: C33, 1958.
226. Travis, L. E. *J. Exper. Psychol.* 21: 302, 1937.
227. Trömner, E. *Deutsche Ztschr. Nervenh.* 105: 191, 1928.
228. Verzeano, M., D. B. Lindsley and H. W. Magoun. *J. Neurophysiol.* 16: 193, 1953.
229. von Economo, C. In: *Handbuch der normalen und pathologischen Physiologie*, edited by A. Bethe, G. von Bergmann, G. Embden and A. Ellinger. Berlin: Springer, 1926, vol. 17, p. 591.
230. von Economo, C. *Ergebn. Physiol.* 28: 312, 1929.
231. Walker, A. E. *Congr. latinoam. neurocir., Montevideo* 6: 926, 1955.
232. Walter, W. G. *J. Neurol. & Psychiat.* 1: 359, 1938.
233. Wiggers, C. J. *Physiology in Health and Disease.* Philadelphia: Lea, 1937, p. 250.
234. Wikler, A. *Proc. Soc. Exper. Biol. & Med.* 79: 261, 1952.

CHAPTER LXV

# Perception

HANS-LUKAS TEUBER[1] | *Psychophysiological Laboratory, New York University-Bellevue Medical Center, New York City*

CHAPTER CONTENTS



[1] The preparation of this chapter has been aided by the Commonwealth Fund of New York, and by the U. S. Public Health Service under their program grant M-3347 to the Psychophysiological Laboratory.

IT MAY SEEM STRANGE to find a chapter on perception in a handbook of neurophysiology, doubly strange if the chapter begins with the claim that there is no adequate definition of perception and ends with the admission that we lack a neurophysiologic theory. The two difficulties have a common source: physiologists distinguish sensation from perception and deal with sensory processes, in different modalities, as dependent upon receptor mechanisms and subsequent neural events. As a result, perception assumes the role of some supplementary higher process, superimposed upon these sensory capacities and devoid of any obvious neural correlate. After excluding perceptual phenomena from sensory physiology, we are thus hard put to explain how different sense modalities interact in perceiving, how we apprehend shapes or sizes, distance or depth, or, more broadly put, how things manage to look, or feel or sound the way they do (284).

In the absence of an accepted definition and theory of perception, any selection from its vast literature will be arbitrary. Yet we shall try to stress those phenomena which reveal the inadequacy of traditional distinctions between sensation and perception, and those problems which seem most in need of physiologic interpretation. We shall deal, first, with subjective intensity and psychophysics in order to show that, even here, where simple one-to-one relations between stimulus and sensation are assumed to exist, there actually arise complex issues that require a new approach to our search for physiologic correlates. The same issues will be raised with regard to the more traditional topics for students of perception: the problems of perceived shape, depth and motion, the constancies and the illusions.

None of these topics can be covered completely, but we shall attempt to concentrate throughout on those perceptual phenomena that can be demonstrated not only in man, but in lower forms. Correspondingly, we shall try to stress methods for studying perception that might be applicable to a wide variety of vertebrate and even invertebrate species. This is done in spite of the risk of seeming capricious in our choice of experimental evidence. The comparative approach permits one to utilize naturally occurring differences of neural structure in formulating guesses about the way in which neural structures might determine perceptual performance. Moreover, the problems of pattern vision in monkey, octopus, or bee will seem less remote if one realizes that the nervous systems of infrahuman forms are available for experimental intervention not permissible in man and that the greater simplicity, especially of invertebrate neural organization, may let us discover correlations between structure and function that might go undetected in the study of human subjects.

In contrast to the usual picture drawn by surveys of comparative sensory physiology, most of the phenomena we shall note cannot be interpreted in terms of known physiologic mechanisms. These unexplained effects are presented, nevertheless, because they may suggest directions in which the search for neural bases of perception should proceed.

Our effort at reviewing these phenomena might be justified if we remember that the facts observed in any field are largely a function of the questions that are being asked. Understanding of neural activity "is likely to progress more rapidly if we keep before us the facts of behavior which we hope eventually to explain" (308). If perceptual phenomena continue to be refractory to neurophysiology, one might wonder whether current approaches to 'basic' sensory processes are correctly conceived.

The difficulty may be analogous to the one raised by phenomena of complex coordinated movements (see Chapter LXVII by Paillard in this volume). As

long as one's efforts are concentrated on reflex mechanisms of the spinal cord, the problems of patterning of skilled movements seem residual and nearly insoluble questions, relegated to some 'highest integrating activity' of the central nervous system. The very fact, however, that patterning should thus remain unexplained casts serious doubts on the adequacy of current theories of coordination on spinal as well as supraspinal levels (531).

The distinction between sensory and perceptual processes, and the preoccupation with the former at the expense of the latter has historical rather than logical reasons. We can trace the origin of this distinction by considering, first, a problem which cuts across individual modalities of sensation, the problem of measurement of sensory intensity and quality (psychophysics).

## PSYCHOPHYSICS

### *Reduction of Sensory Qualities*

The traditional distinction between sensation and perception and the resulting difficulties have a long history [admirably treated by Boring (53)]. Empiricism has always been sensationism; experience could not be acquired except through the senses, and the senses could not err except for erroneous interpretation of their unequivocal message. Sensations were elementary conditions of learning, while perceptions were complex and learned; they were considered as compounds in which present sensations gained their meaning through related residues, 'images,' 'ideas' of previous sensory events [see Berkeley (38)]. Yet the sensations, so conceived, were actually postulates of classical physics.

From its renaissance beginnings, physics has systematically restricted its data by reducing the qualitative richness of everyday sensory experience to certain quantifiable aspects of matter and of matter-in-motion. Galileo established physical acoustics by suggesting that perceived pitch might be reducible to frequencies of vibration in a medium such as air or water. [See Galileo Galilei (141); the Galilean discovery was communicated two years earlier by his correspondent Mersenne (344).] Newton analogously referred perceived differences in hue to corresponding differences in vibrations of the ether, likening these to vibrations of air which "according to their several bignesses, make(s) several tones in sound." He did so in spite of his increasing preference for a corpuscular theory of light; in fact, his curious insistence on seven primary colors was based on an explicit analogy to the seven tones within the octave (361). The progressive elimination of sensory qualities in physics culminated in the nineteenth century,[2] and it was at that time that 'psychophysics' arose as a systematic effort to reintroduce the 'lost' qualities through a special form of experimentation. The very form of these experiments at first reinforced the distinction of sensation and perception.

### *Attempted Restitution of Qualities in Psychophysics*

In the typical psychophysical procedures of the nineteenth century, as formulated by Weber (523), Fechner (122), von Helmholtz (501) and Wundt (551), attributes of sensation, such as pitch, were explored by systematic variation of a single physical dimension, such as frequency, as if pitch were the perception of the frequency of a tone. Thus, a one-to-one correspondence between physical and sensory dimensions was assumed, although Weber (523) had already established that such a correspondence was not linear: for any given intensity of stimulation, $I$, the just noticeable difference, $\Delta I$, was known to vary with the intensity of stimulation; where $I$ was small, $\Delta I$ tended to be small; where $I$ was large, $\Delta I$ tended to be large; in fact, Weber believed that one might formulate a law: $\Delta I / I$ = constant (Weber's law).

For instance, in judging differences of weights placed successively on the finger, the just-discriminable difference (or, as we now say, the Weber fraction) was thought to be approximately constant at 1/30. From Weber's law, Fechner derived, by integrating, the expression $S = K \log I$ (Fechner's law) where $S$ is the magnitude of sensation, measured in some appropriate unit, and $I$ the stimulus measured in terms of physical units defining the absolute threshold.

This simple logarithmic relation between stimulus and sensation cannot be valid if just-discriminable differences of sensation are unequal, i.e. Fechner's law cannot hold if Weber's law is incorrect. The evidence, available for many sensory dimensions,

[2] It could be argued that classic physics, by eliminating most aspects of everyday experience from its primary data, elevated somatic sensation to the status of prototype of all sensation; mechanics implies action and reaction through contact, especially if forces acting at a distance are denied. The much greater abstractness of modern physics is accomplished by abandoning any attempt at reconciling the structure of physical reality with that of perceptual phenomena.

tends to show that Weber fractions are only very approximately equal; over a given range of stimulus values, the Weber and Fechner expressions are usually least adequate at the extremes of the range. Moreover, recent developments in psychophysical scaling methods[3] [see Stevens (451)] suggest that Fechner's logarithmic expression might have to be replaced by a power function.

As Stevens points out, the systematic measurement of sensation in relation to a given stimulus dimension can be performed without recourse to the concept of differential thresholds and without assuming the constancy of such differences. When a picture in black and white is viewed, first in the sunlight and then in the shade, we ordinarily perceive little, if any, change in the relative brightness of its features. This could mean that the differences in brightness have remained the same under changing illumination (as Fechner might have said) or, alternatively, that the ratios of light and dark portions have remained unaltered. The assumption of constancy of subjective differences would lead to the formulation $\psi = k_1 \log \varphi$ (a restatement of Fechner's law) in which the psychological magnitude $\psi$ is related to the logarithm of a physical dimension $\varphi$, and a constant $k_1$. If we assume, instead, that the proper relation is based on equal ratios, we obtain $\psi = k_2 \varphi^n$ (power law of Plateau and Stevens) where $n$, the exponent, varies with sense modality and stimulus dimension.[4]

The procedures employed in verifying the power law involve the use of a psychophysical method in which the observer is asked to adjust a light (or a sound) to half or one fifth, etc., the brightness (or loudness, etc.) of a standard. For over a dozen sensory continua, these ratio methods have resulted in power functions, that is the subjective magnitude is roughly proportional to the stimulus magnitude raised to a power. The values for the exponent $n$ cover a considerable range. For loudness, the exponent is 0.3; for the subjective intensity of electric shock to the fingers, it is 3.5 (451). The apparent subjective magnitude of an artificial 'star' grows roughly as the square root of the photometric level.

These bare figures do tell us a good deal about the differences between various sensory dimensions. For apparent loudness, where the exponent is around 0.3, there is enormous compression of the scale of magnitudes, since in order to double the apparent loudness, we must multiply the physical energy by 10 (or the sound pressure by the square root of 10). For the 'unphysiologic' mode of stimulation by direct electric shock to a subject's finger, the converse is true; here, the subjective intensity shoots up as the 3.5 power of the current applied—a fact to bear in mind when applying direct electrical stimulation to peripheral nerves. But whether the organism compresses or expands a given stimulus dimension, the basic psychophysical relation would be simple: equal stimulus ratios produce equal subjective ratios (451).[5]

### *Multidimensional Nature of Sensory 'Attributes'*

Whether logarithmic or exponential, these psychophysical relations suggest a simplicity of sensory processes which would seem to set them apart from the complexity of everyday perception of objects. This impression of simplicity, however, is deceptive. The classical attempt at restitution of sensory qualities, as we termed it, presupposes the existence of independent one-to-one relations between sensory and stimulus dimensions. But if pitch is nothing else than perception of frequency, or hue of wavelength, it would be difficult to understand in what sense Galileo or Newton made discoveries about these physical correlates of sensation. The fact is that psychophysical relations need not be one-to-one, or isomorphic in the sense that to each definable physical dimension there corresponds one and only one sensory dimension. This lack of parallelism has such far-reaching implications that it needs to be considered here in some detail.

For Wundt, each sensation had two 'attributes,' viz. its specific quality and intensity (551). To this meager inventory, extension in space and duration in

[3] The classic methods employed in establishing quantitative relations between stimulus dimensions and sensations are reviewed and illustrated in Boring (53); more detailed descriptions of recent developments in these psychophysical methods are given in Woodworth & Schlosberg (549, pp. 192–266). See also Stevens & Galanter (453). Stevens' methods have been criticized by Garner (143).

[4] An exponential, rather than logarithmic, relation of stimulus dimension to sensory dimension has been anticipated by Plateau (384) who conjectured the 'power law' after he had asked eight artists to paint, independently, a gray halfway between extreme white and black. The grays turned out 'presque identiques' and remained so under different illuminations. Later in his career, Plateau retracted his views, primarily under the influence of certain psychophysical experiments by Delboeuf (69). [See Stevens (451).

[5] Attempts at identifying electrophysiologic correlates of sensory scales [e.g. Granit (168)] must be reconsidered in the light of psychophysical evidence which shows the inadequacies of the Weber-Fechner formulation.

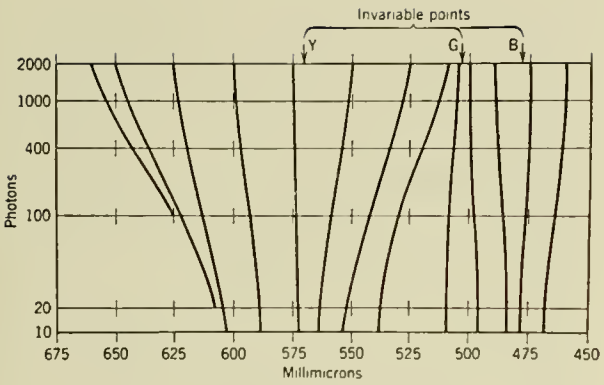



FIG. 1. Contours for constant hue. A given contour describes the combinations of wavelength and intensity of a monochromatic light which yield impressions of equal hue. Only three points within the visible spectrum are 'invariable,' i.e. show no shift in apparent hue with changing intensity. Except for these invariable points (a yellow at 572 mμ, a green at 503 mμ and a blue at 478 mμ), all other points vary in a predictable fashion according to the Bezold-Brücke effect. There is a fourth invariable point which is not shown, since it lies outside the spectrum, being constituted by a specific mixture of long and short waves, in the purple. [From Purdy (391).]

time were added by Külpe (296), and his four attributes of sensory quality, intensity, extensity and protensity (duration) have guided the search for neural correlates of perception for more than half a century. There is, however, no reason why this should be so. Consider the case for vision. Here, a basic sensory quality would be color (perceived hue), ordinarily thought as corresponding to wavelength (or mixture of wavelengths); the intensity dimension would be represented as perceived brightness. Yet, with few exceptions, hue is not only dependent upon wavelength, but upon intensity; except for certain invariable points in the spectrum, all colors shift in hue towards either yellow or blue as the intensity is increased. This phenomenon of shift in hue with changing intensity—the Bezold-Brücke effect—can be quantified by plotting contours of equal hue (see fig. 1) which describe the combinations of intensity (in photons) and wavelength (in millimicrons) which will yield equal-appearing hues [see Purdy (391)]. Perceived hue, thus, is a joint function of wavelength and intensity. Correspondingly, perceived brightness is a joint function (although a different function) of the same physical dimensions; even a casual glance at a spectrum will reveal that different wavelengths, although energy is constant, have different-appearing brightness within the spectrum. Moreover, when over-all energy is reduced, the relative brightness of the different colors shifts in accordance with the Purkinje phenomenon. (Characteristically, this Purkinje shift fails to appear in the rod-free part of the retina.)

We thus have ample evidence for the dependence of hue on both wavelength and energy (as the Bezold-Brücke effect shows) and for brightness, again, on energy and wavelength (as the Purkinje effect shows), although two different functional relations establish these two psychological dimensions, hue and brightness. Lest there be a suspicion of some lingering pre-established harmony (two physical for two psychological dimensions), we might consider a third psychological dimension of colors, saturation. Saturation, too, varies with wavelength (being minimal in the spectral yellow and violet) and with energy (being maximal at intermediate energy levels), so that we can get three systematically discriminable aspects of color sensations out of the appropriate combinations of only two physical (stimulus) dimensions [see Boring (51)].

The situation has considerable generality. In audition, perceived pitch is easily identified with frequency, and loudness with intensity of sound waves. Yet for pure tones, one finds an analogue of the Bezold-Brücke effect since perceived pitch changes as intensity is changed, even though frequency is held constant. Low-frequency tones, when raised in intensity, sound lower in pitch, while high-frequency tones sound higher in pitch when their intensity increases (450, 561). There even is an 'invariable point' which falls roughly into the region of maximal sensitivity along the frequency spectrum. As a result, we can plot contours of equal pitch (fig. 2) which indicate the changes in frequency that need to be made in order to counteract the alterations in pitch produced by a given change in intensity.[6]

But loudness, too, is a joint product of frequency

[6] Happily for instrumental music, the shifts depicted in fig. 2 are found in this pronounced fashion only for pure tones, but much less for the complex 'timbered' tones produced by musical instruments. It is not clear whether this relative constancy of pitch for complex tones is due to the presence of harmonics or whether other factors play a role. However, the phenomenon of greater pitch constancy of these complex tones belongs to the large group of effects called 'perceptual constancies' discussed below. It should be remembered, in this context, that the statements about color sensations made in the preceding sections are similarly restricted in scope; they apply primarily to 'film' colors, i.e. colors which do not in any obvious way belong to the surface of seen objects. [See Katz (249, 251).]

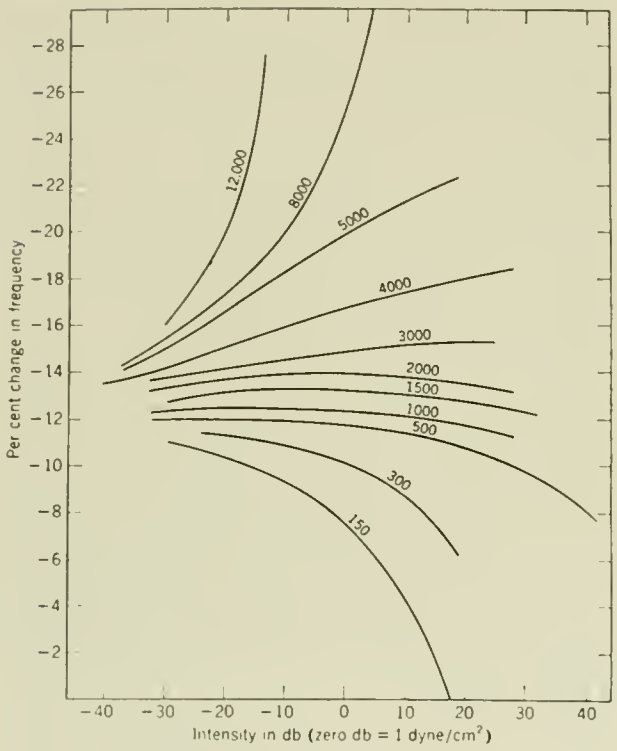



FIG. 2. Contours for constant pitch. A given contour describes the combinations of frequency and intensity of a pure tone which yield impressions of equal pitch. The *ordinate* was arranged so that a contour with positive slope shows how pitch increases with intensity (for high frequency tones). [Based on data from Stevens (450).]

and intensity. The equal-loudness contour (449) indicates, for a standard tone of low frequency, how intensity has to be changed to balance changes in frequency in a comparison tone so that the comparison tone appears to equal the standard in loudness (see fig. 3). In addition, figure 3 shows that at least two other psychological dimensions, 'volume' and 'density,' can be obtained by appropriate covariation of frequency and intensity.

It is apparent from these sets of contours that two dimensions on the physical (stimulus) side can yield more than two perceptual dimensions. Moreover, a perceptual dimension is not established by independent variation, as used to be believed in the classical psychophysics of the nineteenth century (551). It is actually impossible to vary any of the dimensions depicted in figure 3 in isolation, that is without varying the others. What we have, instead, is a case of 'dependent constancy,' or invariance; we can maintain a percept by appropriate variation of all of the other relevant perceptual dimensions. The concept of in-

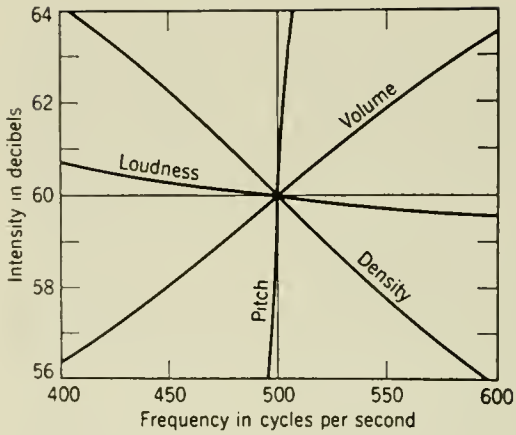



FIG. 3. Isophonic contours for pitch, loudness, volume and density. Each contour defines the combinations of frequency and intensity at which a comparison tone will be perceived as equal in pitch or loudness, or volume, etc., to the standard tone of 500 cps and 60 db. [From Stevens (449).]

variance will assume increasing significance as we progress to other problems of perception in this chapter.

### *Implications for Neurophysiologic Studies of Perceptual Processes*

There are at least three lessons that may be derived from this brief review of nineteenth- and twentieth-century psychophysics. They concern *a*) the stage in the nervous system where sensory differentiation occurs; *b*) the complexity of sensory processes which makes their separation from perception problematic; and *c*) the need for uniform methods—an enlarged psychophysics—to attack together what used to be treated separately as sensory and perceptual phenomena.

We have seen that the organism can respond differentially to sensory stimulation in such a way that the responses can have more dimensions than the stimulus itself. Different functions relating frequency and intensity of sound yield at least four sensory attributes, and perhaps more. If this is true, then our search for neural bases of such differentiation should proceed with great caution; clearly, the differentiations may occur at any stage, from the periphery (the receptors) to the final paths antecedent to the discriminating motor responses. Thus, it should not be surprising to find an organism making discriminations which appear to go beyond the differentiation in its peripheral receptors. Nor need one assume that

all differentiations of which a receptor structure is capable ought to be preserved in later stages within the nervous system; differentiation made possible at the periphery may be lost at some subsequent stage. The absence of color discrimination in the cat may be a case in point, since the cat retina appears to make color discriminations even though behavioral evidence for such discriminations on the part of the 'whole cat' is lacking (see Chapter LX by Neff in this volume).

If sensory discriminations, according to the views developed here, no longer bear a simple one-to-one relation to the stimulus dimensions, then one of the stronger nineteenth-century arguments for separating sensation and perception is lost. In the new 'dimensional' psychophysics, sensations have a complexity not unlike that of perception, even though the earlier attempts at separation have not been entirely abandoned. Consider the classical psychophysical procedures: the matching of a monochromatic color with a dichromatic mixture, the determination of just-discriminable differences along a particular stimulus dimension, the discovery of absolute thresholds. In all these procedures, the hoped-for simplicity of results was marred by 'errors'; matches between stimuli differed, depending on whether the standard stimulus was placed to the left or right of the variable ('space errors'); stimuli were over- or underestimated, depending on whether they were given first or second in a successive comparison ('time errors'); judgments of weights differed markedly, depending on the presence or absence of much lighter or much heavier weights in the series submitted for comparison ('intraserial effects'). All these phenomena, though interesting in their own right, tended to be treated as sources of 'error' in strict psychophysical experiments; they were to be canceled by balancing the stimulus presentation so that effects of spatial position, or temporal order, or of constitution of the series could be eliminated. There is, of course, nothing illegitimate about such attempts at controlled experimentation; but the distinction between the intended results as 'primary,' or 'sensory,' and the space or time effects as 'errors,' produces rather than proves the elementary nature of sensation. At the same time the study of perception becomes an exclusive concern with these 'errors' which are left over, as it were, as mere residuals after the more serious business of sensory psychophysics has been accomplished.

Actually, intraserial effects and related phenomena can be dealt with just as rigorously as the supposedly more elementary threshold phenomena. Helson's work on 'adaptation levels' (197) shows that the subjective magnitude of a singly presented stimulus depends upon the weighted geometric mean of the series of stimuli that the subject has worked with; but, as in all psychophysical procedures, explicit or implicit verbal instructions are crucial since they determine which stimuli are perceived by the subject as forming part of the series. [However, Stevens' protest (452) should be noted.] That this is so, can be demonstrated very simply. Ask a subject to move a particular weight out of the way (with the excuse that it is cluttering up the table), and this particular weight will not enter into the formation of the series; it will have no effect on the subjective magnitude of the other weights within the test [see Brown (65); also Bruner (71)]. The purity of the psychophysical experiment thus depends largely on the perceptual set (71) adopted by the subject, and the distinction between sensory and perceptual aspects of the task is spurious.

Beyond the consideration of space and time errors, and of intraserial effects, perception studies in the later nineteenth century were primarily concerned with two sets of phenomena, the so-called 'illusions' and 'constancies.' To this day, these have remained central problems in perception. Every textbook shows samples of some geometrical optical illusions—the famous Müller-Lyer pattern, for instance (see fig. 34)—and most texts list the special theories developed to account for these effects [cf. Boring (53, pp. 238–245), Woodworth & Schlosberg (549), pp. 417–423)]. Yet to speak of illusions as special cases—curiosa of perception, as it were—is tendentious. As soon as one admits that perception lacks simple one-to-one correspondence to physical stimuli, the explanation for perceptual illusion will be sought among the general laws of perception. Once these laws are known, the illusions themselves will be understood (53).

The same may be said for the so-called constancies, e.g. the relative constancy of perceived brightness, size or shape, with varying illumination, tilt or distance. The classical treatment of these effects as results of 'unconscious inference' by von Helmholtz (501) implies that we ought to be able to perceive the 'image' on our retina, and then elaborate our perception by recourse to some judgmental factors into a corrected or interpreted view of the distal object to which the image refers. But to assume that we ought to 'see' the retinal image may be just as naive an assumption as the belief that in hearing a given pitch, we ought to perceive a frequency. The very notion of a retinal 'image' is a curiously anthropo-

morphic way of describing the receptor processes which antedate perception.

Although the 'unconscious inference' theory of von Helmholtz has been revived in some of the current studies of perception from the 'transactionalist' viewpoint [see Ames (7), Ittelson & Cantril (236)], the prevailing approach to the 'constancies' and to the 'illusions' is based on the belief that nearly all perception is perception of objects, and that the constancies pervade perception on all levels, from the most elementary to the most complex.

### *Impact of Gestalt Psychology and Operational Behaviorism*

This unitary approach to perception can be credited largely to two sources: first, to Gestalt psychology (and phenomenology) and second, to certain trends in operational behaviorism. The Gestalt psychologists, notably Wertheimer (536), Köhler (269) and Koffka (284), from the outset rejected all notions of elementary sensory processes. To hear a pure tone or to see a single contour meant to them to perceive organized structures, and they considered it their task to search for the laws underlying all perceptual organization. In this respect, they continued the tradition of phenomenology—the careful description of sensory experience. In such descriptions, errors of perception were not features to be eliminated; they were to be studied as clues to the basis of normal function. Thus, Purkinje (393) was convinced that "illusions of the senses tell us the truth about perception" ("dass Sinnestäuschungen Gesichtswahrheiten sind"); and he recorded the manifold phenomena of entoptic imagery—the illusions produced by inadequate stimulation of the retina. Hering (200, 202), the main antagonist of von Helmholtz, surveyed phenomena of simultaneous and successive contrast, of afterimages and memory colors, demonstrating that a patient study of sensory phenomena leads to the discovery of many problems for sensory physiology which a more rigid psychophysical approach would unavoidably pass by.

It is clear that such phenomenal distinctions are based on consensual validation, an appeal to introspections of the other man. In modern behaviorism appeals of this sort are proscribed; the tendency has been to reduce all studies of perception to that of sensory discrimination. As Boring (53) has pointed out, this tendency, too, results in a denial of any dichotomy between sensation and perception; in behaviorism, sensation (in the form of discrimination) has absorbed perception, while in phenomenology and Gestalt psychology, perception has absorbed sensation.

### *The Need for Converging Operations*

The reduction of perception to discrimination has not gone without contradiction within the framework of modern behaviorism itself. Thus, Garner *et al.* (144) have pointed out that to reduce perceptions to the overt discriminatory responses by which they are observed would seriously restrict the scope of experimentation. The reduction of perception to discrimination is usually defended by operational behaviorists, such as Graham (166), by referring to Bridgman's critique of concepts in physics. For Bridgman (61), "a concept is synonymous with the corresponding set of operations," i.e. the experimental operations by which the concept is established. However, this does not mean that any operation will generate a meaningful concept. If one thinks of perception as intervening between stimulus and response, and thus distinct from either of these two terms, it is obvious that a particular kind of operation is needed to establish whether a series of events is perceptual in nature. This can be done, as Garner *et al.* (144) suggest, by means of converging operations. These are any sets of two or more independent experimental procedures which lead to the same terminus, i.e. establish a concept by ruling out alternative interpretations.

To take an example from a currently popular area of experimentation consider the supposed difference in perception of words, or of drawings, or symbols with different emotional content [e.g. McGinnies (342)]. In a hypothetical experiment of this type, four words are exposed at high speeds (i.e. tachistoscopically) and the subject is required to recognize them. If two of these words are neutral, and two vulgar, the result will be that the neutral words are read at high speeds, while the vulgar words are not, or at least not until their exposure has been made quite long. Such a result is commonly interpreted as perceptual defense, since failure to read is considered identical with failure to perceive. However, the failure to report vulgar words may be a characteristic of the subject's responses rather than his perceptions. A converging operation would be to pair vulgar responses with the neutral stimulus words, and vice versa (144). Only under these conditions could one decide whether the 'defense' was, in fact, perceptual. It should be noted that both operations are needed if one cares to estab-

lish whether the defense was a mere withholding of unpopular responses or a truly perceptual effect.

The need for converging operations is particularly pressing in work on perception in young children or in animals below man. In the absence of verbal report we have to depend entirely on differential motor reactions on the subject's part, but this does not mean that any given set of these reactions is sufficient to reach conclusions regarding the subject's perceptual repertoire. Earthworms will pull pine needles into their burrows by grasping them at the base (where the pair of needles hang together). Conversely, they pull leaves into their burrows by grasping the tip, never the stem, so that the leaf rolls itself into a tube as it disappears into the burrow. This highly adaptive behavior looks like form perception, but the basis of discrimination is gustation [cf. Mangold (338)]. The worms avoid powdered extracts of the base of leaves and ingest powdered extracts of the tips, and conversely for pine needles.

Thus, converging operations are needed to define the sensory basis of discrimination; moreover, any tendency to reduce all perception to discriminatory responses would reintroduce the classical sensory bias and force us to omit all those problems from consideration which are crucial in developing a physiologic theory of perception.

## SOME CENTRAL PROBLEMS FOR A THEORY OF PERCEPTION

What are those perceptual phenomena which the traditional physiology of the senses has left out? It is difficult to make a complete list, but we can enumerate half a dozen aspects of perception which any physiologic theory would have to take into account. These aspects are, briefly: *a*) patterning, *b*) selectivity, *c*) reaction to relations or ratios of stimulation, *d*) reaction to similarity, *e*) apprehension of serial (temporal) order, and *f*) equivalent reactions to certain spatial and temporal sequences [cf. Lashley (308)].

### *Patterning*

Perception is patterned, since some parts of a stimulus array are always perceived as belonging together while others are not [cf. Schumann (415)]. We tend to see (or feel) 'things,' and not the holes between them [cf. Koffka (284)]. Temporal sequences are analogously structured into events [cf. Johanssen (241)]. Such patterning would imply, as its neural counterpart, an interaction of concomitant and successive processes in afferent systems. Interaction between different sense modalities is perhaps a special form of this general patterning of perception. The difficulty here is not the interaction as such, but its organization—the how and why of interaction—in direct analogy to the problems of coordinated movement.

### *Selectivity*

Perception is selective. Although the structuring of what we perceive is largely determined by the actual distribution of stimuli in an array, we can selectively attend to one part as against others (see fig. 14). Such selectivity, in neural terms, would probably amount to some preliminary priming or sensitization (308), favoring one part of a neural system over others and hence one way of structuring a complex sensory input over its alternatives. Another, and currently attractive, view would assign a special role in this selection or filtering to extralemniscal afferents (245, 324), or to efferent pathways to sense organs (139, 140, 168, 203, 204).

### *Reaction to Relations*

Perception is relational, that is the organism reacts to ratios of excitation rather than absolute amounts. A classic instance of this is the case of 'transposition' of learned reaction to size differences [cf. Köhler (266)]. Once trained to select the larger of two stimuli (e.g. two squares, *a*, 10 cm and *b*, 20 cm in height), the subject readily selects the larger member of another pair of stimuli in which all dimensions have been doubled (thus, he will choose $b'$, when $a' = 20$ cm and $b' = 40$ cm). There is little difficulty in constructing models of central nervous activity that would incorporate this feature, but most speculations about the neural basis of discrimination (see Chapter LX by Neff in this volume) either have ignored it, or have tried to reinterpret these phenomena in Pavlovian terms by invoking principles of conditioning and of 'primary stimulus generalization' (374). Considerable ingenuity has been displayed in these reinterpretations [cf. Spence (434, 435) and Hull (226)], but the attempts have not been convincing [for critique, see Klüver (259), Lashley (304), Hunter (227, 228), Rudel (407, 408) and others] and are contradicted by some experimental evidence (162, 464). Thus, a child or animal (chick, monkey or chimpanzee) can be trained to select an object of inter-

mediate size among three objects differing in size; having learned to do so, the subject can, under some conditions, 'transpose' this middle-size reaction to a new set of objects of greater or lesser absolute size (162, 407). Apparently, most discriminations involve responses to relationships between the discriminanda.

*Similarity*

Closely related is the central problem of similarity in perception. As Mach (333) pointed out, geometric similarity is not necessarily identical with optic (or, more generally, perceived) similarity, since we cannot predict, on the basis of purely physical characteristics of a stimulus, which patterns will be perceived as similar.[7] Stimuli are similar in some respects and not in others so that the problems of similarity involve all those listed up to now, patterning, selection and transposition. Perception of similarity is basic to our capacity for recognition, and thus for inclusion of what we see or hear or feel into classes of stimuli. What the neural basis of such classificatory activity might be has not even been a matter of much speculation [but see Semon (419), Craik (94), Hebb (188) and MacKay (335)]. Some guesses about it would be needed in understanding agnosia, a condition claimed to consist of a specific loss or impairment of this classificatory activity in the presence of particular brain lesions. As we shall see, however, there is considerable controversy as to whether agnosia, in this sense of the term, could ever occur.

*Serial (Temporal) Order*

A great deal of work on perceptual phenomena has been restricted to the study of static patterns, usually visual displays in two dimensions. While these patterns serve to underscore the importance of grouping and perceptual selectivity, undue reliance on these static demonstrations leads to a neglect of temporal sequences in perception, the problems of serial order. In most languages, the sequence of words in a phrase conveys specific meaning, and the sequence of phonemes within a word has crucial importance in all forms of human speech (see Chapter LXVIII by Zangwill in this volume). The apprehension of such patterns of successive stimulations clearly requires some temporary storage of the information received at any one moment (62, 64), and capacity to deal with the completed sequence as if it were a simultaneous pattern.

*Equivalence of Certain Temporal and Spatial Patterns*

Lashley (307) has pointed out that within limits we can apprehend a visual (or tactile) configuration, irrespective of whether we explore it by scanning, part for part, or whether we see it 'at one glance' (or have it impressed upon the skin). The neural basis for this transposition of serial into simultaneous patterns is unknown but would seem to require some central mapping of temporal into (simultaneous) spatial orders.

If we look back upon this list of problems, it will be apparent that they are interdependent. Nor is it likely that the listing is exhaustive (5, 21, 489, 490). Yet enumeration of these half dozen aspects of perception should remind us of the existence of problems which traditional physiology has rarely considered. The list may also help us to indicate a striking similarity (in logical structure) between two seemingly unrelated fields: experimental embryology and the psychophysiology of form perception. In both areas, the origin of form is a central problem. In both, clues for analysis can be derived from essentially three sources: studies involving defect, isolation, or recombination (530). In defect experiments, the development of organic form (or perception of patterns) is investigated in the presence of a lesion in the structure. In isolation experiments, the behavior of a part of the structure is studied after it has been cut off from the remainder of the living system, or the entire system is studied under conditions of artificially diminished input. In recombination studies, finally, one inquires into effects of altered arrangement in the spatial relationships of parts, as in embryologic experiments involving transplantation (433, 530), or in studies of vision after inversion of eyes in fly or fish or newt (348, 436, 439), or after the prolonged wearing of distorting or inverting spectacles in man (285, 455–457; Held, unpublished observations). We shall therefore turn next to a review of normal pattern perception, especially the problems of shape, selec-

[7] Take the riddle of octave similarity. To most listeners, tones one octave apart are more similar than are tones within the octave, and tones differing by an octave are readily confused. Perhaps Newton's preoccupation with the musical octave was not so strange after all, although it remains odd that he gave octave structure to the visible spectrum. The anthropomorphic character of this attribution is underscored by the difficulty of showing octave similarity in animals below man [although there are data suggesting that octave similarity exists for rats (48)].

tivity and transposition, and their implications for studying motion and depth perception, illusions and constancies. To each of these sections, we shall add the corresponding discussions of altered perception following defect, isolation or recombination of parts.

## PERCEPTION OF SHAPE

### *Basic Aspects of Figure Processes*

MINIMUM ARTICULATION, ASSIMILATION AND CONTRAST. Perhaps the best way to begin a survey of the role of patterning in perception is to consider those rare situations where patterning is minimal. The classical demonstration for this in the visual modality is the homogeneous field, or *Ganzfeld* [see Metzger (345) and Koffka (284)]. The subject looks into a half-sphere which has been painted a uniform gray or white. If illumination is lowered to the point where the subject no longer sees the texture of the walls of this sphere (its microstructure), he does not perceive any surface but a mist of undefined depth. Similar effects can be obtained by an ingenious variation of the method devised by Hochberg *et al.* (217). The observer wears eyecaps made from halved table tennis balls fitted over the eyes. Under these conditions, even the view of his own facial structures is excluded. Colored transillumination of these eyecaps leads, in most instances, to a complete fading of any experienced hue, an event postulated by Koffka (284), although brisk eye movements or interruptions of the illumination can transiently restore the impression of color. These *Ganzfeld* demonstrations suggest that perception is dependent on some articulation of the stimulus array; in fact, absence of such articulation leads in many subjects to visual hallucinations. These observations should be considered in interpreting electrophysiologic studies of retina or cortex where the stimulating fields employed are often devoid of structure.

Static articulation of the visual field, however, seems insufficient, unless the texture of the field moves relative to the eye. Even during fixation, fine movements of the eye transport contours continuously over the retina [see Ratliff & Riggs (394)]. While these involuntary motions do not seem to play the role in the maintenance of acuity that was attributed to them by Marshall & Talbot (340), they nevertheless seem necessary for the maintenance of vision. Stabilization of the retinal image is followed by disappearance of contours[8] and the appearance of a mist of undefined depth.

Curious effects are obtained when a *Ganzfeld* of the original type (345) is modified by the introduction of a gradient of illumination, so that one lateral half receives more light than the other. If the gradient remains below threshold at any one point, the perceptual effect is that of a uniform brightness intermediate between those of either side; the gradient as such is not perceived. If, however, a shadow line is cast across the field, separating the lateral halves, each half is immediately seen as possessing a characteristic brightness, one darker, the other brighter, with a 'step' along the contour, although each half to either side of it is still seen as uniform within itself. Such a sequence of events illustrates a tendency towards assimilation (homogeneity) in the absence of contours, and the opposing role of contrast where contours are formed [see Krech & Crutchfield (293)]. An analogous demonstration is given in figure 4.

The lateral interactions within the visual field involved in assimilation and contrast can be demonstrated on many phylogenetic levels and may have electrophysiological correlates in the eyes of the horseshoe crab (183). Behavioral demonstrations of contrast effects have been extended throughout the vertebrate series from chimpanzees (171) to fish (206), and have been accomplished for such diverse invertebrate forms as butterflies [*Macroglossum stellatarum* (263)] and scallops [*Pecten* (495)]. While assimilation and contrast are potent factors in the perception of shapes, they are not sufficient in themselves to produce shape or figure processes.

FIGURE AND GROUND. It was the Danish psychologist Edgar Rubin (406) who proposed that a basic aspect in the formation of shapes was their perception as a 'figure' against a 'ground.' He described and illustrated primitive visual figures as 'standing out' with object character [and hence surface color, according to Katz (249, 251)] against their backgrounds which seemed to possess film color, and were often seen as if extending behind the figure itself. Thus, the contour dividing figure and ground is perceived as belonging to the figure. Numerous attempts were made by

[8] Such stabilization has been achieved in two ways: *a*) by Ditchburn & Ginsborg (107) who mounted the visual targets on a stem rigidly connected with a contact lens and *b*) by Riggs *et al.* (404) who employed an optical system including a front-surface mirror mounted on a contact lens. By either of these methods, image stabilization is accomplished since there is no relative motion between the visual display and the eye.

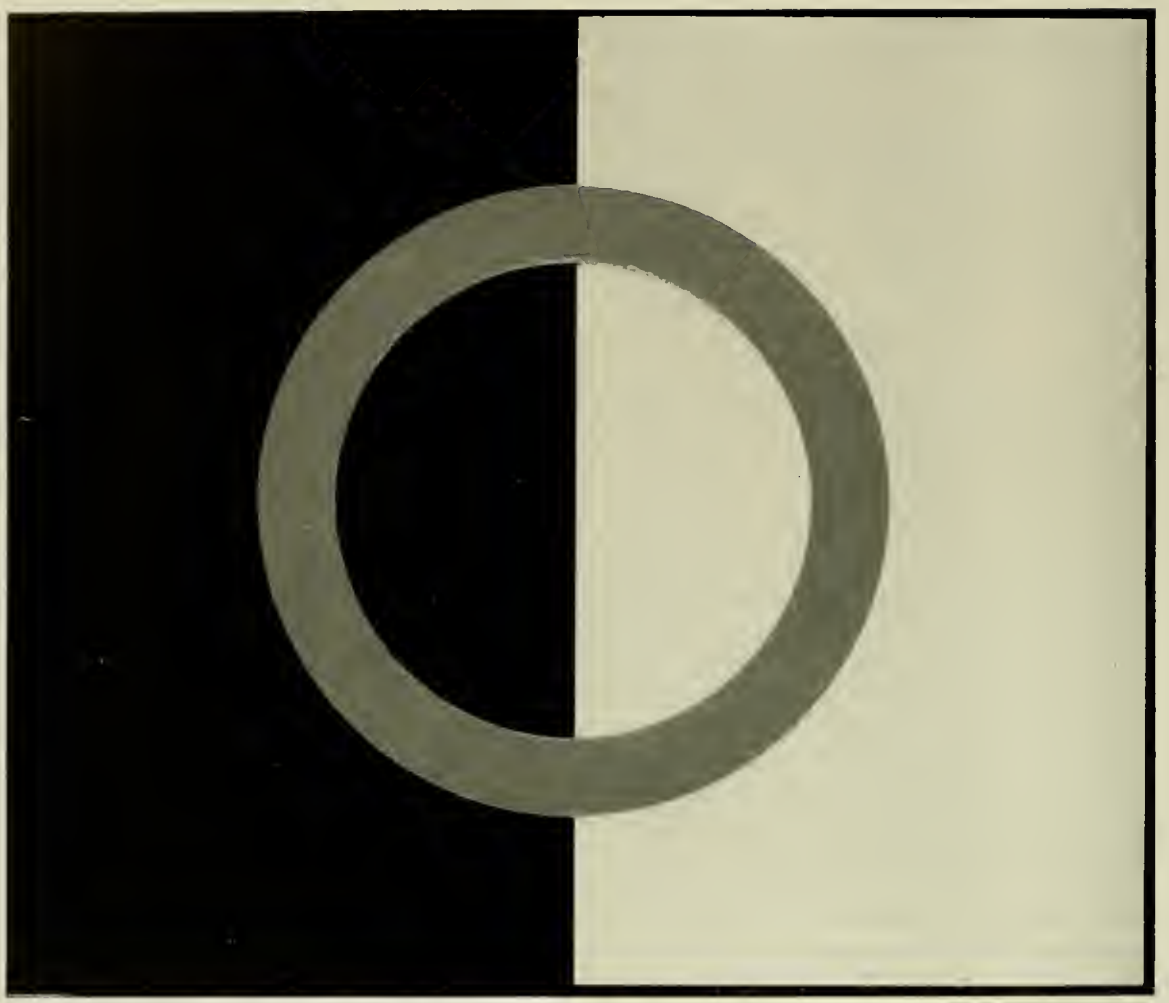


FIG. 4. A configuration illustrating assimilation, contrast and the role of boundaries in structuring a visual field. Bisect the gray ring by placing a pencil across it, vertically, and note the abrupt darkening of the right half of the ring, and the increase in brightness of the left half, by moving the pencil to the left or right, contrast can be 'drawn' from one side to the other. [Based on Koffka (284).]

Rubin himself and others such as Wertheimer (537) and Musatti (356) to define the stimulus determinants which decide what part of a pattern will become figure and what part ground. It is often, but not always, the enclosed portion that assumes figure character, but a complete enumeration of factors has never been achieved.

It is possible to make the stimulus situation ambiguous so that what is figure can also be seen as ground and conversely (fig. 5); it is under these conditions of greater or lesser ambiguity that subjective determinants (attitudes, past history) on the part of the perceiver can play their role in determining what is seen. Although the figure-ground principle was first developed for the somewhat artificial situation of bidimensional patterns on paper, it probably holds for tridimensional visual objects and seems to have its analogues in other sensory modalities (250, 553). The general importance of the figure-ground principle is underscored by the observation that ambiguous figures are apparently not recognized by most subjects if on second presentation their figure-ground articulation has become reversed (406).

PRINCIPLES OF GROUPING. What determines figure formation in a stimulus array? Wertheimer (537) has derived a series of principles of grouping or phenomenal laws, the most important being those of proximity, similarity and 'good figure.' These 'laws' of grouping have been severely criticized. For one,

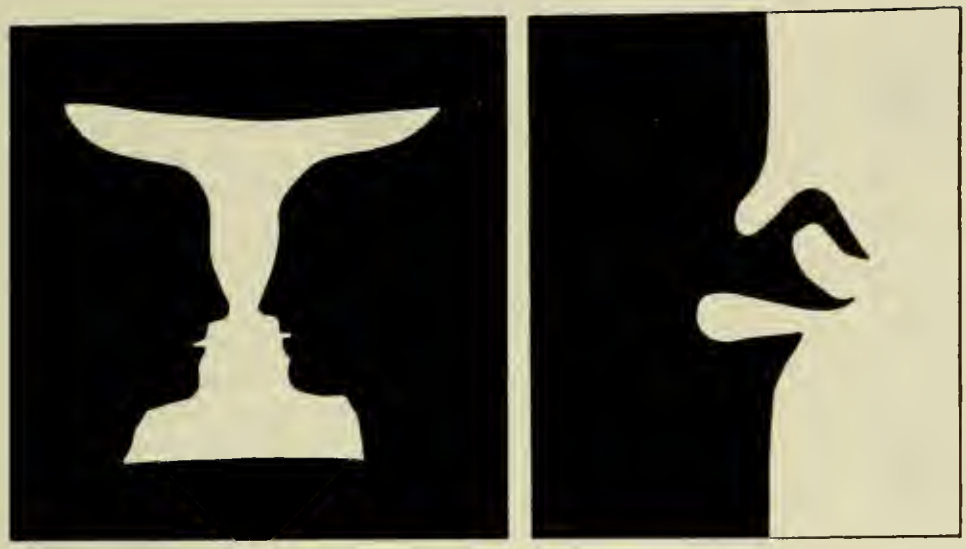


FIG. 5. Figure and ground. *Left*, white goblet or black faces (Rubin's vase-figure); *right*, black claw or white protrusions. [From Rubin (406).]

their universality has been questioned; their validity might seem to be limited to line drawings or similar visual patterns. There is, however, some evidence that these principles transcend the situations and sense modality from which they were derived. A fundamental aspect of figure perception—relative ease of 'tranposition'—was first described for auditory patterns; a melody can be recognized whether sung by a bass or soprano, or transposed from one key to another (496). Similarly, a shape remains recognizable, within limits, in spite of variations in overall dimensions, color and background, or whether presented to the sense of sight or touch.

The early work of the Gestaltists has stressed these facts of transposition rather than their limits, but these limits merit more systematic study. Melodies become unrecognizable when played backwards, and there seem to be serious restrictions in intermodal transfer, e.g. in identification of visual with tactile patterns (292).

The most urgent objection, however, to application of Gestalt principles in perception is their nonobjective and nonquantitative character which makes specific predictions of perceptual events so difficult. There is, however, no obvious reason why this difficulty should not be overcome. Rigorous psychophysical methods can be applied, as has been done by Bobbitt (50) in dealing with the principle of closure, or by Heise & Miller (191) in dealing with auditory patterning. It is here that information theory may be profitably applied, particularly in specifying the structure of the stimulus array. Thus, Attneave (11, 12) has given an ingenious method of serial guessing of the component parts of visual patterns in analogy to Shannon's technique (422) for estimating the redundancy in message sequences. A figure is the 'better,' the smaller the number of sequential guesses needed to specify it.

A final objection to Gestalt principles in perception, as they are usually stated, comes from those, such as Hebb (188), who believe that form perception is learned. Gestalt psychologists, by stressing the ubiquity of the principles of grouping on different ontogenetic and phylogenetic levels, have tried to show that these principles antedate learning (560); in fact, Köhler (267) rejected their designation as 'innate,' because he believed that these principles reflect basic physical aspects of the brain processes which correspond to perception. If the regularities revealed by these principles are simple physical laws, then they are prior to, and independent of, the development of organic form.

By contrast, modern empiricists have tried to show that perceptual patterns have to be acquired laboriously during normal ontogenetic development. For Hebb (188), perceived forms have some 'primitive unity' (his term for figure-ground articulation) prior to learning, but this unit formation does not, he believes, suffice in mediating shapes. Shape is acquired in early infancy through successive scanning of contours by eye movements which are guided reflexly along predominant brightness gradients in the visual

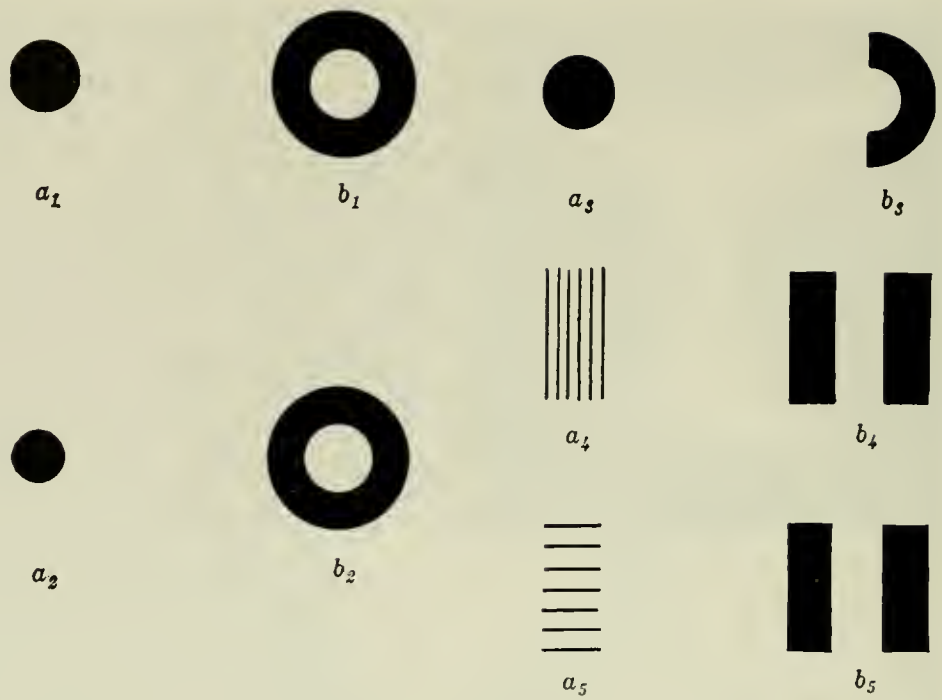



FIG. 6. Forms used in experiments on metacontrast (successive interaction of contours). Figures marked *a* are not perceived if they precede figures marked *b* within critical intervals, and if their outer contour coincides with the subsequent position of the inner contour of the *b* figures. [Modified from Werner (534).]

field. Repeated scanning movements lead to organized neural traces, or 'cell assemblies' [due to some process similar to Kappers' neurobiotaxis (247)]; eventually, the scanning movements as such can drop out, since parts of the figure will now activate the trace and the corresponding perceptual habit of seeing (or feeling) a given form. Transposition of forms (the ability to recognize them independently of size or of orientation on receptor surfaces) would likewise be acquired in early development. An indirect argument in favor of these views is sometimes seen in the difficulties of pattern perception under various conditions of 'reduced' stimulation, under low illumination, with small visual angles or with brief periods of time (as on tachistoscopic presentation).

Tachistoscopic exposures can impede the perception of patterns to such an extent that one might doubt whether patterns are ever perceived under normal conditions so that apprehension of different parts is strictly simultaneous. Apparently some scanning is necessary even for 'good' figures. In fact, ease of perception under reduced conditions, such as tachistoscopy, can be used as still another objective index for goodness of a figure. This rank order of difficulty of shapes under abnormal exposure conditions has been explored, and the results fitted to a physical diffusion model of shape perception by Bitterman *et al.* (46) and Krauskopf *et al.* (291).

That shape perception takes time can be demonstrated even more strikingly by successive tachistoscopic presentation. If the two patterns shown in figure 6, disk and annulus, are exposed each for 12 to 20 msec., and the annulus follows the disk at a critical interval of about 150 msec., the disk will not be perceived. For the effect to appear, it is necessary that the inner contour of the annulus occupy the same region of the visual field as the outer contour of the disk. If the order of succession is reversed (annulus shown before disk), both patterns are seen. Apparently, the outer contour of the disk is still in the process of formation when the surrounding annulus begins to form. The phenomenon has been known for a long time under the name of 'metacontrast' [see Stigler (454) and later Werner (534)]; it has been reported to occur when the first pattern is presented to one eye, and the second to the other eye, but there

is no adequate quantitative comparison of the monocular with the binocular conditions.[9]

Possibly a variant of this procedure is the wipe-out phenomenon which results when an information-bearing visual stimulus (e.g. a triangle) is flashed tachistoscopically, and followed within critical time by a white flash, with appropriate time-relation. The first (figured) flash cannot be reported; it has been 'wiped out' by the bright field which followed (324). Unfortunately, this effect seems to appear only if both exposures are given to the same eye; it is thus possible that the second (unfigured) flash serves merely to obliterate an afterimage that would normally appear and assist in the perception of the briefly exposed pattern.

*Ontogenetic Considerations*

Our knowledge of shape perception in children is surprisingly scant, and a good deal of the work is contradictory. It has been asserted that children show the effect of the 'laws' of grouping more than adults; or, differently put, that they can overcome these effects less (e.g. by selective attention to detail, set or instructions). Thus, hidden figures (like those illustrated in fig. 14) are difficult to unscramble for children; in fact, most of the patterns developed by Gottschaldt (164, 165) present insoluble perceptual tasks for children below the age of six, according to Witkin (542) and Ghent (148). There also are marked individual differences in the performance of adults in this respect (542). As Ghent (148) has pointed out, the crucial source of difficulty may be the sharing of contours; the young child is disproportionately handicapped whenever the contours of the embedded figure also form integral contours of the embedding configuration. By contrast, the partial concealment of figures by intersecting lines ('mixed figures') presents less difficulty to normal children (fig. 7).

According to Stern (447, 448), children below the age of six are less disturbed than adults in recognizing patterns shown to them in unusual orientation (e.g. upside down). Such an observation would weigh against the views of Hebb (188), since it would imply greater rather than less transposability of shape at younger ages. Actually, the evidence is unclear. Children who cannot read often look at drawings in picture books which they hold upside down; their own drawings may show orientations on the page which are peculiar from the adult standpoint (377). Yet more recent studies (229, 230; Ghent, unpublished observations) indicate that children may have more (not less) trouble than adults in identifying inverted pictures. Their preference for holding picture books in peculiar ways may be related to consistent positional preferences which they exhibit just as strongly when presented with unfamiliar geometric patterns.

A weakness of many of the available studies of child perception is their failure to employ converging operations. The indices of a particular perception are often drawings made by the children [cf. Eng (113), Volkelt (493) and Osterrieth (372)], which preclude decision as to whether the peculiarities lie in the child's perceiving, in his drawings, or in both. Less ambiguous results can be expected from systematic application of identical methods for the study of form perception in children and in nonverbalizing sub-

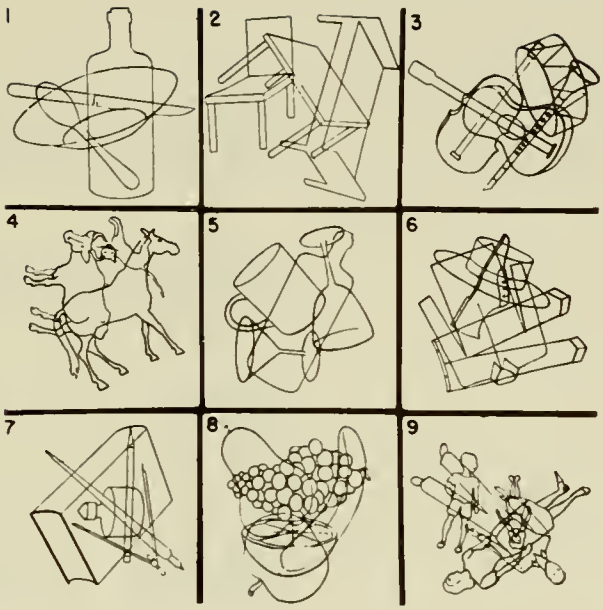



FIG. 7. 'Mixed figures' employed in testing normal children and those with brain injury. Each of the nine composite drawings was presented individually and without the numbers shown. [See Teuber (465); illustrated subsequently in Ghent (148).]

[9] The phenomenon gains in interest in view of recent demonstrations that resolution of successive light flashes at cat or monkey optic cortex (where it is measured by discrete evoked potentials) can be improved by intercurrent electrical stimulation of the midbrain reticular formation (324). Microelectrode recordings for individual neurons of the optic cortex of the cat have revealed a similar effect; trains of light flashes are followed by discrete neural discharges at higher than normal rates if reticular formation or nonspecific thalamic nuclei are intercurrently stimulated (245).

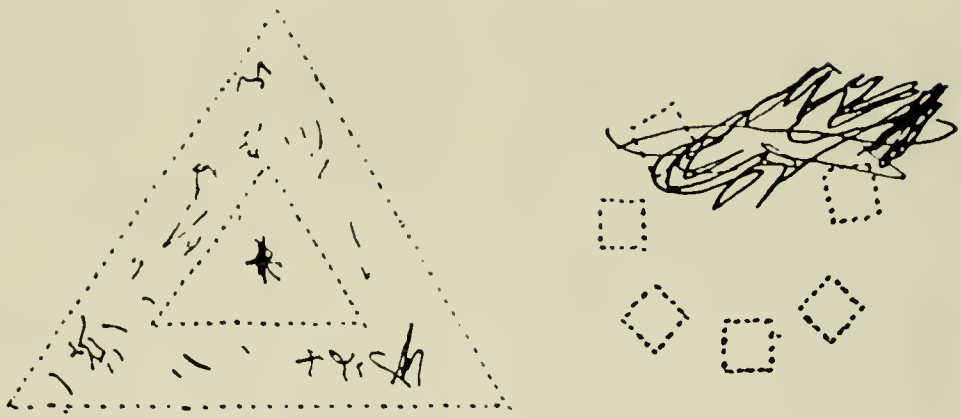


FIG. 8. 'Drawings' produced by a chimpanzee. The experimenter provided the animal with the regular outlines shown, and the animal scribbled over them, filling interspaces and 'completing' designs which the experimenter had deliberately left unfinished. [From von Schiller (510).]

human forms, as has been done by Rüssel (409) and Gellerman (147).

An obvious, but again, little explored difference between children and adults is the marked difficulty children have with apprehension of peripherally exposed figures and with tachistoscopy. That children require a much longer exposure time for the perception of patterns has been adduced in favor of the view that pattern perception is learned (188), but alternative interpretations are possible. Apparently, the two sources of difficulty, limited peripheral span and increased time requirements, interact in some complex fashion. It is known that even with unlimited exposure children take much longer than adults in surveying an array of patterns, and brain lesions in children produce disproportionate slowing in searching time, according to Teuber *et al.* (468). Piaget has suggested that children may have virtually a tubular field, and some of the peculiarities of their perceptions can perhaps be understood in these terms (148).

*Phylogenetic Considerations*

Discovery of neural correlates of pattern perception will be made more likely if we can define some of the essential similarities and differences that exist between pattern perception in man and various other species. We are very far from such a goal.

VERTEBRATES. Work on subhuman primates by Köhler (270) and Klüver (259) has disclosed puzzling resemblances among the perceptions of monkeys, anthropoid apes and man. Most revealing in this respect is Klüver's systematic survey (259) of equivalent responses in monkeys. Klüver's method involves presenting the animal with a pair of discriminanda (e.g. a triangle vs. a circle), and then varying these stimuli until the learned choice breaks down. This method thus defines ranges of similarity or equivalence of stimuli; it reveals that all of the patterns which are functionally equivalent (i.e. elicit the same response) in the monkey look similar to man.

Analogous conclusions are suggested by the analysis of figural preferences in the scribbling of chimpanzees studied by von Schiller (510). These scribblings, to be sure, are never representational drawings, but they can be influenced by the figural properties of visual patterns placed on the paper by the experimenter prior to letting the animal scribble over it (see fig. 8).

Lashley (301) has extended Klüver's technique of 'equivalent and nonequivalent stimuli' to the study of pattern perception in the rat. Apparently, rodents as well as primates tend to group stimulus arrays into figure and ground. Figures that are easily discriminated by man are also 'easy' for monkey and rat, and stimuli lacking identifiability for one species are also readily confused by the other, as shown in figure 9 (301). These similarities (of perceived figural similarity) were so surprising that Lashley considered but rejected the possibility that results might have been different if rat and not man had constructed the test patterns. Comparable data on lower vertebrates are scant [see, however, Pache (373) for frogs and Herter (206) for fish] but offer no support for assuming any abrupt changes in the evolution of vertebrate pattern vision.

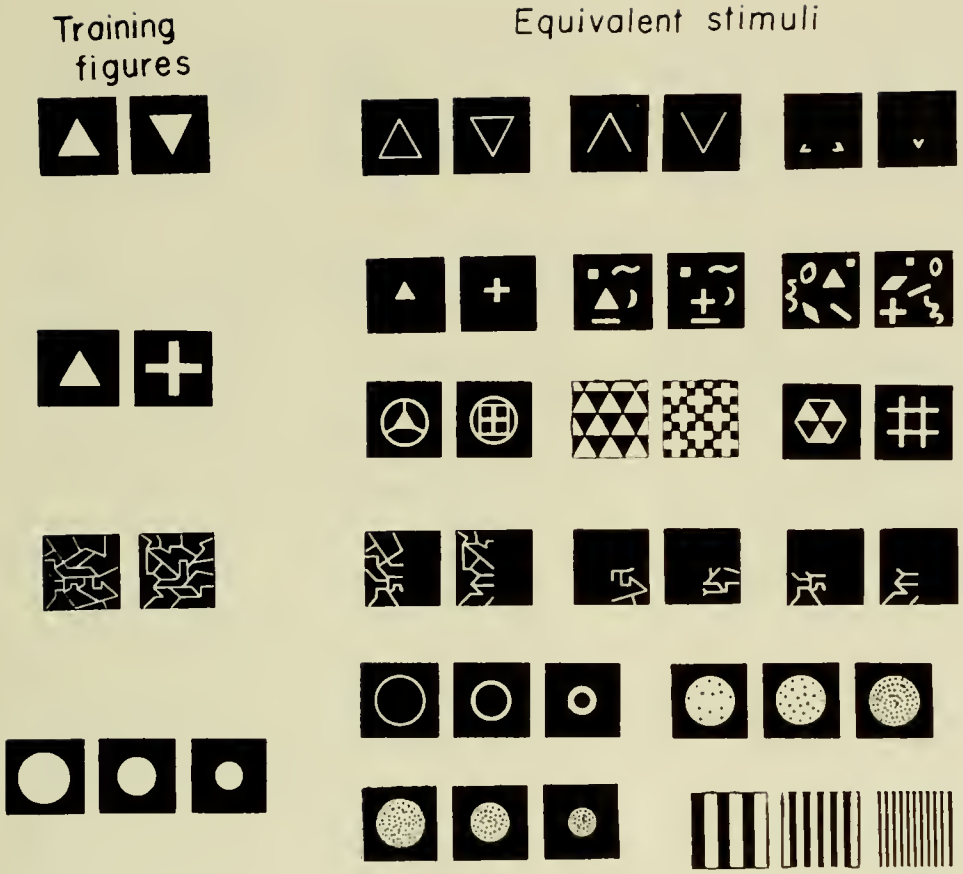



FIG. 9. Equivalent-nonequivalent stimuli, designed according to Klüver (259) and used by Lashley (301) to establish range of perceived similarity in rats. Trained to select, say, the solid upright triangle shown in the *top row* of the training figures, the animal will transfer its choice to the corresponding outlines of an upright triangle and even to incomplete outlines. Thus it will select, on successive presentations of pairs of test stimuli (in *top row*), those shown to the *left* in each pair. The same applies to the training figures shown in the *second*, *third* and *fourth rows*, and to the corresponding arrays of test stimuli. On actual presentation of training or test figures, lateral positions of rewarded and unrewarded patterns are randomized, so that the rat cannot solve these problems by acquiring simple left- or right-going tendencies.

There must be some differences. Although positive evidence is hard to find, one might search for these differences in two directions. *a*) There are some indications that lower animals may show narrower limits in transfer from one learned discrimination to other discriminanda, and *b*) conversely, under certain natural conditions lower animals may show nondifferential reactions to stimuli that for man are obviously different. To take the first possibility first: Lashley's rats failed to transfer reaction from a white triangle (on a black ground) to a black triangle (on a white ground), a transfer possible for monkey, ape and man. (Note, however, our difficulties with the identification of faces in photographic negatives.) Similarly, rats are less tolerant of rotation of figures—an isosceles triangle is not equivalent to the same triangle rotated 90°; there are similar though lesser difficulties on such transfer tests for apes and for human children (147).

The other possible source of data for species differences lies in observations such as Buytendijk's (83) who showed for toads how the range of perceptual equivalence (perceived similarity) expands or contracts in particular directions depending on the animal's internal state. A toad is placed into a cage with inanimate objects, such as matches and strands of dried moss. As long as the hungry animal has not received any food, it does not react to these objects. After it has eaten a worm, it begins seeking the broken

matches, and after it has eaten a spider, it begins picking up the moss.

In ethology, the systematic study of species-specific behavior [cf. Tinbergen (486)], attempts are made to assess internal states or 'moods' in animals by surveying the range of equivalent reactions to varied dummies as stimuli (*Attrappenversuche*). Thus, mobbing reactions in small birds can be elicited by balls of feathers on a stick. The resulting observations are sometimes interpreted as if they suggested the existence of particular schemata or kernel perceptions which act as releasers of particular behavior sequences [IRM, 'innate releasing mechanisms'], for example those of courtship, especially in birds [see Huxley (232)] or of predator recognition (486). There is controversy about the generality of some of the observations [cf. Hirsch *et al.* (216) and Tinbergen (487)], and particularly about the innateness of the reactions. The most radical claim in this respect is implied in other recent descriptions of bird orientation. For the warbler, a night migrator, Sauer (412) has reported accurate orienting reactions to stellar constellations (including the artificial constellations in a planetarium), and this in birds which had been reared in isolation and without any previous exposure to the starry sky.

Phenomena of animal camouflage provide strong indications for similarity in pattern vision among different vertebrate species [cf. Thayer & Thayer (480)]. There, the principles of perceptual grouping (272, 537) turn into rules for concealment, as in the construction of hidden figures (142, 164, 165). Experimental proof for the efficacy of protective coloration, or cryptic attitudes (93) is available in a few species, for camouflaged insects as prey (85) and fish and birds as predators (458, 554). The evidence suffices to establish that these concealing features act at least as strongly for lower vertebrates as they do for man, indicating that perceptual principles involved in grouping and in camouflage antedate the evolution of the human nervous system. Some species differences, however, might lie in the relative ease with which concealment can be overcome; conceivably, lower forms are less able to override these factors by selective attention, but evidence on this point is sparse.

This review of pattern perception in children and subhuman forms reveals the fragmentary state of our information. The available methods have not been used sufficiently to establish valid comparisons between species. It is often forgotten that the same species that can be shown to react to broadly schematic stimuli in some situation (as stressed by the ethologists) can also be trained, in the laboratory, to make refined perceptual distinctions.[10] Even within a given species we usually lack systematic studies defining both the extent of equivalence (generalization) and of discrimination. These limitations will become still more obvious when we turn to a review of pattern perception in the higher invertebrates. Does perception in these forms differ as much from that in the vertebrates, as the differences in the nervous systems of the phyla would suggest?

HIGHER INVERTEBRATES: CEPHALOPODS. Studies of pattern vision in higher invertebrates with large image-forming eyes (such as the octopus) again suggest a rather puzzling similarity in visual organization between these forms and vertebrates. Experiments involving successive discrimination [cf. Boycott & Young (57, 58)] and transfer to equivalent patterns (461) have revealed few differences, except that an octopus trained to go to an upright triangle will transfer this reaction to a rotated triangle. This is not found in rats (301) nor in pigeons (488), although it does appear in monkeys (358), chimpanzees (146) and children (146). Furthermore, Sutherland (459, 460) showed that the octopus seems virtually incapable of discriminating oblique lines (\ vs. /), even though it learns promptly to tell a vertical (|) from a horizontal (—) line.

This specific difficulty in discriminating mirror images prompted Sutherland to postulate a neural scanning mechanism in the octopus, whereby shapes are classified as follows. The visual impulses are led into an array of cells arranged in rows and columns, and the total excitation is counted separately in columns and rows. Reaction to shape is then determined by ratios of horizontal to vertical excitation, a mode of determination which would make horizontal and vertical maximally discriminable, and oblique lines not at all (459–461).[11] As Sutherland himself points out, Lashley (301) had noted a similar tendency to confuse mirror images in rats.

Quite recently, Rudel (unpublished observations) has shown that normal children below age six have

[10] That these discriminations are not only the product of artificial settings is indicated by the role of individual recognition among birds in the maintenance of pecking orders. Disturbances in the pecking order of chicks (Leghorn fowl) are most readily induced by changes around the head or by abrupt changes in body color. If the changes are gradually introduced, they have no effect [see Guhl & Ortman (174)].

[11] The same mechanism would account for equivalent reactions to identical shapes of different sizes, a reaction found for the octopus (461), pigeon (488), rat (301) and monkey (259).

FIG. 10. Figures used in testing form perception in honey bees. The bees could be trained to distinguish each of the figures in the *upper row* from each in the *lower row*, but failed to distinguish among those in the *upper row*, or among any of those in the *lower row*. [Modified from Hertz (207).]

analogous difficulties with mirror images; thus, they failed to learn a distinction between ⊏ and ⊐. (However, Rudel's finding that ⊏ and ⊐ are practically indistinguishable for small children, while ⊔ and ⊓ are easily discriminated, does not seem to conform to Sutherland's hypothetical scanning mechanism, nor would it seem to be predictable from an earlier theory of shape recognition advanced by Deutsch (103). (More recent observations by Sutherland himself indicate that for octopus, too, there is much less difficulty with ⊔ and ⊓ than with ⊏ and ⊐, although the difference between the two tasks is not as great as in the child.)

An incidental outcome of Sutherland's work is a new and more convincing interpretation of Boycott & Young's well-known report of altered memory for visual form in the octopus following extirpation of the vertical lobe system from the animal's brain (58). Such animals tend to lose discrimination, and attack both positive and negative shapes.[12] However, some of the animals can be retrained by presenting shapes at very short intervals (a situation which interferes with learning in normal animals, since they stop attacking shapes to which they are frequently exposed).

Young and Boycott have interpreted these observations by assuming that the negative memory in animals with verticalis lesions becomes very short-lived, and that it can be maintained only by frequent exposures (every 5 to 10 min.) to the negative shape, even if the shape is not attacked. Since Sutherland (460) has shown that "exposure to a shape tends to reduce the tendency to attack a shape" in the normal octopus, it is likely that "verticalis removal may raise general tendency to attack and that discrimination can only show up when this tendency is reduced, and that this reduction may be brought about by very frequent presentation of shapes."

SALTICIDAE. The octopus and other cephalopods are not the only invertebrates whose eyes are capable of forming single images. The jumping spiders (Salticidae) possess such eyes, and apparently depend on them in courtship and in their recognition of prey (190, 221, 222). Heil's field studies (190) describe visual recognition of dead (and hence, immobile) prey. Such an achievement is unexpected, since it has been assumed that most invertebrates require moving targets for adequate perception. Laboratory studies similar to those in the octopus would be desirable.

INVERTEBRATES WITH COMPOUND EYES. By far the most pressing need, however, is for further elucidation of pattern vision in higher invertebrates with compound eyes. That visual orientation is important in bees has been made clear by von Frisch (499, 500) but the way in which visual patterns are recognized by the bees remains elusive. Hertz, in numerous studies (207–209), demonstrated that bees distinguish star-shaped from closed flower patterns, with preference for those with radiating (and hence, with broken) contours (see fig. 10). Zerrahn (557) showed further that the bees' preference increased directly with increasing numbers of contours within a given test pattern. Wolf (546) found that rotating patterns were chosen in preference to identical stationary ones; flickering sources attracted more bees in direct proportion to the rate of flicker. All these observations seemed to suggest that 'pattern' might reduce to 'flicker,' i.e. the number of ommatidia stimulated in rapid succession as the bee flies over a pattern rich in black-white contrast.

This cannot be the whole story, however, since von Frisch had shown as early as 1914 [see also Knoll (264) and Friedländer (133)] that bees can be trained to distinguish bipartite disks (e.g. one lateral half blue, the other half yellow), depending on the right-left pattern (e.g. yellow-blue vs. blue-yellow). Such an accomplishment in an animal with compound eyes is all the more remarkable if one recalls the inability of the octopus to distinguish mirror-image patterns. Even more puzzling are the demonstrations by Hertz (210) that with some patterns, bees can be trained to

[12] Although this effect is often quoted as being specific for visual perception, it exists just as well for tactile discrimination in a blinded octopus lacking the vertical lobe (533).

choose the one with fewer contours. Some most unexpected features of visual perception in bees, finally, are implied in certain open-field experiments on the 'clustering' of bees at food sources [see Kalmus (246)]. It is well known that bees congregate at flowers or food dishes wherever there are other bees. This clustering can be enhanced by placing a mirror below the food source, and even more by placing 'supernormal' (i.e. outsized) cardboard dummies of bees around the food dish. Clearly, the analysis of pattern vision in bees and in other invertebrates with compound eyes is in need of much further study [see also Ilse (234)].

*Changes in Perception of Shape After Cerebral Lesions*

In comparing perception across species one hopes to find differences in function that might correspond to known differences in structure. As we have seen, the differences in perceptual repertoire of different species are on the whole less marked than the similarities. Studies of perception in the presence of defects in neural structures aim at finding characteristic changes as the result of ablation, injury or disease. Yet, here too, lack of change or resiliency of perception is a major finding. Nevertheless, there are certain alterations in perception after cerebral lesions that may cast light on the normal bases of perception. As in the phylogenetic studies, however, evidence for these changes can be no better than the methods employed in analyzing their nature. In this respect, methods developed in testing nonverbalizing organisms turn out to be useful in assessing performance in man with brain injury; conversely, studies of animals with experimental ablations profit from tasks derived in clinical settings (466). In the following, we shall briefly consider effects of total removal of primary (cortical) projection systems, then effects of subtotal lesions within these systems, and finally changes found after various lesions encroaching on neocortical structures outside the primary projection fields.

EFFECTS OF TOTAL REMOVAL OF 'PROJECTION SYSTEMS.' For the visual system, it is generally agreed that total destruction of the geniculostriate sector results in total and irreversible loss of pattern vision (see Chapter LX by Neff in this volume). This is believed to take place, whether the lesions eliminate the lateral geniculate bodies, or the optic radiation, or the visual cortex. It is not clear whether in man some reactions to light may eventually return (see, again, Chapter LX). In the experimental monkey, bilateral occipital lobectomy abolishes pattern vision, but reactions to luminous flux are preserved (261). The question of residual vision in man after complete destruction of striate cortex will remain unanswered until testing methods such as Klüver's are applied in suitable clinical cases.

Likewise, we may need to reinvestigate the traditional belief that effects of total striate cortex removal on pattern vision are progressively less severe as one moves down the phylogenetic scale (339). The condition of rodents and carnivores following such an operation may not be as different from that of primates as has been claimed. In still lower forms, differences undoubtedly appear. Removal of the entire forebrain in fish is said to have no effect on visual discriminations whether established pre- or postoperatively [see the review by Herter (206)]. The status of visual capacity in birds following forebrain removal is puzzling and badly needs further examination. Visser & Rademaker (491, 492) report that pigeons without forebrains avoid vertical but not horizontal strings in their path; they alight on the back of a cat while they are in flight, but avoid cats while walking, etc. What is needed is an extension of available testing techniques to the study of decerebrate birds (and of birds with lesions of the optic tectum). If there are phyletic differences in visual organization, then homologous removals of central nervous system tissue in different species would not be expected to lead to homologous changes in perception.

The loss of shape perception in primates following visual cortex resection may have parallels in the disorders of auditory patterning, in primates and carnivores, after certain bilateral removals of 'auditory cortex' [see Diamond & Neff (104) and Chapter LX by Neff in this *Handbook*]. Definition of the minimal effective lesion in the auditory system, however, is difficult because of the uncertainty regarding the full extent of auditory projection fields in carnivores and primates. This difficulty is even greater in the somatosensory system [cf. Cole & Glees (92)] where total loss of reactions to tactile patterns after restricted cortical removal has not yet been demonstrated experimentally, irrespective of whether the subjects were primates, carnivores or rodents.

EFFECTS OF SUBTOTAL REMOVAL IN MAN. Partial destruction of the visual cortex in man is followed by a variety of symptoms which may cast light on neural correlates of pattern vision. There are two outstanding features of residual vision in such defective visual

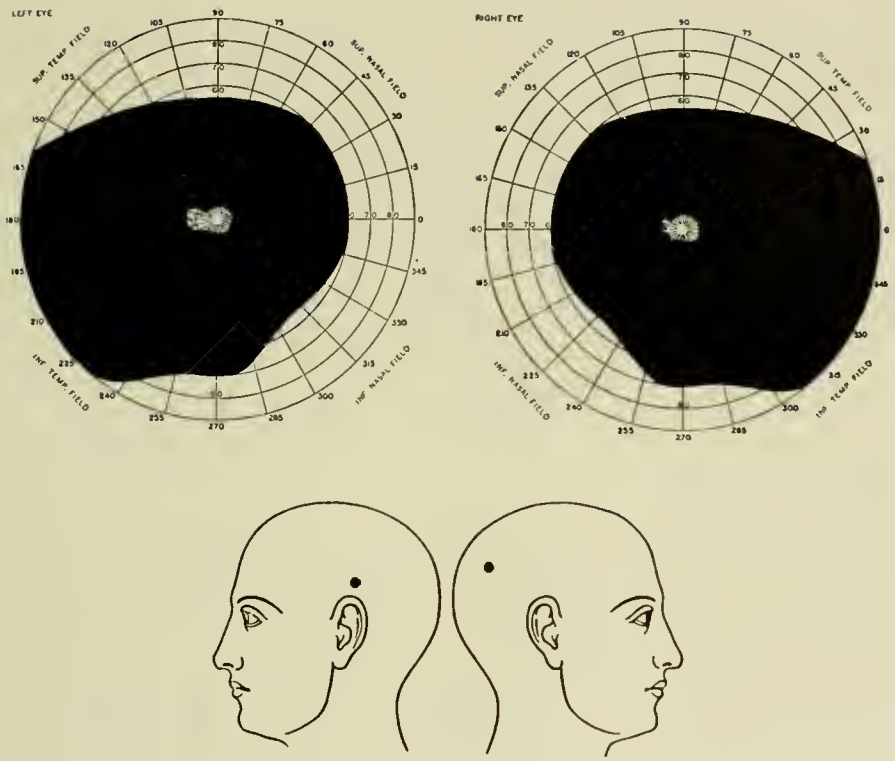



FIG. 11. Complete loss of peripheral field (bilateral hemianopia) with sparing of central vision, following penetrating missile wound of the brain. The course of the projectile is indicated in the *diagrams* below the visual fields in order to show the similarity between this case of 'peephole vision' and an earlier one reported by Holmes (218). This patient showed no obvious difficulties with form perception in the remnant of his visual field. [From Teuber *et al.* (469).]

fields, the resiliency of pattern vision as such (which can be mediated by small remnants of the visual cortex) and the subtle but significant changes in patterning after lesions even of moderate size.

Visual patterns can be perceived in cases of very extensive field defect. The two complementary examples shown in figures 11 and 12 are taken from a study of visual performance after penetrating gunshot wounds of the brain (469). In the first case, a tunnel field, following a through-and-through bullet wound of the posterior lobe substance, was compatible with grossly normal pattern perception in the centrally located remnant of the field. This resiliency is particularly remarkable since the anatomical arrangements in the optic radiations and cortex make it likely that the lesion producing this tunnel field implicated vascular supply to both occipital lobes sparing only the pole. Return of normal pattern vision in the isolated remnant is not easily reconciled with the theory that patterns are recognized by some cortico-cortical interaction between a primary projection field (e.g. here, the visual cortex), and the surrounding 'associative' region (e.g. the prestriate cortex).

Equally remarkable is the capacity, in the second case, illustrated in figure 12, to discriminate large visual patterns (triangles, squares, circles) that are circumscribed around the central island of blindness. Such a capacity is specifically denied by certain theories of shape perception, such as that of Deutsch (103).

The resiliency of shape perception in remnants of defective visual fields should not detract from the observation that there are lasting deficits which merit experimental study. These deficits can be grouped according to their relative specificity (467), i.e. the degree to which they depend on focal lesions in the primary projection system. Thus the scotoma represents a specific and circumscribed loss of shape perception, a gap in the substrate corresponding to a gap in the visual field. After the first year following injury, these areas of acquired blindness remain unchanged in outline, position and density (469). The defects are homonymous and similar in the two monocular fields. In spite of their similarity in the two eyes, they turn out to be incongruent on careful plotting, suggesting that the cell populations which represent each retina beyond the thalamus overlap without being identical. This lack of congruence aside, the scotomata reflect, in shape and position, the specific anatomical arrangements within the visual pathways. It is difficult to conceive of any other consequence of cerebral lesions which would be as static, localizable and circumscribed.

In the presence of these scotomata, however, there

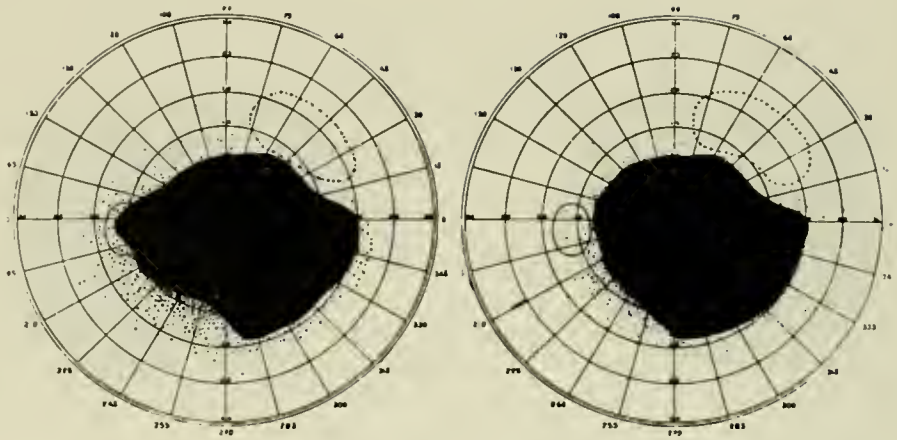


FIG. 12. Central scotoma, surrounded by spared peripheral vision, following penetrating missile wound of the occipitopolar region of the human brain. The course of the missile suggested involvement of upper and lower lips of both calcarine fissures. This patient was capable of distinguishing large forms (triangle, circles, squares) presented so that they surrounded the central area of blindness. [From Teuber *et al.* (469).]

are other changes of a more subtle nature which do not conform to any simple point-for-point correlation of structure and function. If one tests those areas of the visual field which lie outside the scotoma, one finds that shape perception is disproportionately handicapped by tachistoscopic presentation (33, 386). In the same regions of the field, there are other associated disturbances: contours may fade more rapidly; fusion thresholds for flickering light are reduced; and there is impairment of dark adaptation, and of perception of real and apparent motion. These changes involve the visual field as a whole (23, 294, 470–473); in this respect, these changes are less specific than the scotoma since they appear even in those parts of a visual field which seem intact on routine perimetric testing. However, the defects are restricted to cases with circumscribed visual field defects, a fact suggesting that occipital lesions produce twofold effects: those that are focal (scotoma), and those that are less focal, involving visual functions over the entire field and many aspects of visual performance.

COMPLETION AND EXTINCTION OF PATTERNS. These subtle but persistent alterations can be manifested by additional changes in the mode of functioning of the injured substrate. Under a variety of conditions, figure processes are 'completed' across scotomatous regions so that there is no gap in perception although part of the stimulus figure falls into areas of blindness (30, 33, 70, 137, 386, 469). A characteristic instance of this completion or filling-in process is shown in figure 13.

Such a filling-in is well known for the area of the normal blind spot (501), but in that case, completion is usually attributed to the fact that there is discontinuity in the retina but not in the cortex (20). The argument cannot be advanced for completion of patterns across scotomata acquired after cerebral lesions. Moreover, even in the transient scotomata of migraine (303) or of 'visual fits' (469), completion is regularly observed. The phenomenon is thus a basic feature of perception; it is difficult to reconcile with most perceptual theories which invoke a scanning of the cortical projection areas [e.g. Pitts & McCulloch (381)] or with those versions of 'field theory' which assume *a*) that all of the perceptual process takes place in the primary projection field and *b*) that the perception as such is based on an 'isomorphic process' which takes place within the projection field (271, 281). Either a scanning or a field theory would have to be modified in view of these completion phenomena.

As the result of completion, defective visual fields may be functionally more extensive than the distribution of plotted scotomata would indicate. A converse process, however, restricts perception in seemingly functioning regions (29). This is the phenomenon of extinction of patterns in certain areas of a defective field. 'Extinction' occurs in mildly impaired areas of the visual field when other relatively intact areas are stimulated simultaneously. Thus, a pattern may be seen on exposure to an amblyopic half of a field, as long as this exposure takes place against a relatively homogeneous background. However, as soon as a second pattern of any sort is simultaneously exposed in the other (less impaired) half of the field, the first pattern either becomes less distinct ('obscuration') or vanishes altogether ('extinction') (29). As soon as the pattern in the less impaired part of the field is removed, the one in the affected field becomes visible.

The phenomenon has many variants, described by Bender (28). It can occur within a lateral half of a visual field, e.g. between its upper and lower quad-

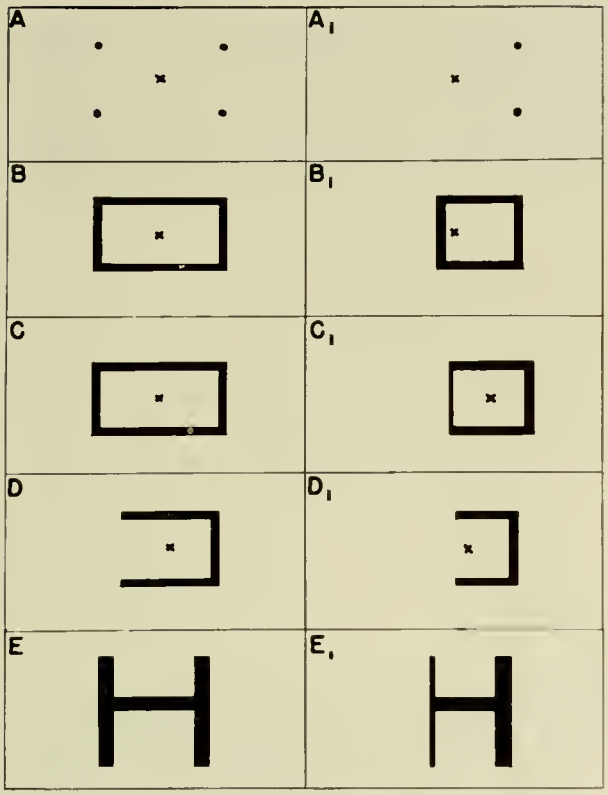



FIG. 13. 'Completion' of forms projected partly into the blind half of the visual field in a case of left homonymous hemianopia. *A–E* are patterns presented on a translucent screen (at 100 msec.) by a tachistoscope; *N*, fixation point. Patterns *A–C* subtended 10° to either side of the fixation point along the horizontal meridian. Patterns *D* and *E*, 7° and 8°, respectively. The patient reported what he saw ($A_1$–$E_1$), first verbally, then by drawings, then by selection from a series of comparison patterns. [From Bender & Teuber (30); see also Teuber *et al.* (469).]

rants. It occurs in the tactile and kinesthetic modality. Thus, a patient with a right parietal lesion may be able to report a contact on his left hand and on his right hand, as long as each hand is stimulated singly. On 'double simultaneous stimulation' of both hands he may report only the contact on his right (the less affected side). One and the same patient may exhibit extinction for touch and vision, or for one or the other modality alone. Unfortunately, it is still not clear why extinction occurs when it does, and why it fails to occur when it does not (295). Right parietal or parietooccipital lesions are frequently found in cases of extinction, but they are not obligatory.[13] It is conceivable that the phenomenon of extinction on multiple simultaneous stimulation represents a special and exaggerated form of normal lateral interactions between contour processes in a sensory field [see Fry & Bartley (135)]. The famous syndrome of Balint (17), in which the patient can perceive whatever he fixates at any time but nothing else, may be another form of extinction, and similar disturbances may play a role in those forms of so-called agnosia in which a patient cannot organize a large array with multiple patterns (121, 547; see also 331).

It is quite obscure where and how these enhanced lateral interactions within a sensory sphere take place. They need not occur within the primary projection field itself; it is tempting to assign some role in these abnormal processes to nonspecific projection systems (324). A possible analogue in normal states (beyond the short-range interaction of contours) is the interference effect on pain by counterirritation, i.e. an intercurrent painful process set off elsewhere in the body. In the auditory sphere, a possible normal analogue would be the inability to attend simultaneously to dichotic messages (two sets of information presented each to one ear) (63, 87, 352; Chapter LXVIII by Zangwill in this volume).

COEXISTENCE OF SPECIFIC AND GENERAL PERCEPTUAL CHANGES. The review of perceptual alterations after subtotal lesions of the visual projection system in man has revealed an obligatory association of specific symptoms (scotoma) with less specific symptoms found elsewhere in the defective field. In addition, one can construct perceptual tasks which are affected in an entirely nonspecific way, i.e. irrespective of whether there are scotomata or not and irrespective of the site of the cerebral lesion. These tasks employ 'hidden' figures in which line drawings are concealed by embedding them in interlacing contours (see above and fig. 14). Cerebral lesions which result in visual field defects produce disproportionate difficulties in

[13] In fact, the earliest demonstration of one-sided 'neglect' on bilateral stimulation was made in experiments on dogs with cortical removals from either the occipital or the frontal lobes. Jacques Loeb (328) showed that such dogs would invariably turn toward meat on their operated side and neglect another piece exhibited simultaneously to the other side of the fixation point. Loeb's method of double stimulation was applied after that in neurologic patients to demonstrate minimal sensory or visual impairment (72, 369, 386). The curious (transient) disregard of stimuli opposite an acute unilateral frontal lesion in dog and monkey has been investigated further by Bianchi (43), Kennard & Ectors (254) and, quite recently, by Welch & Stuteville (532).

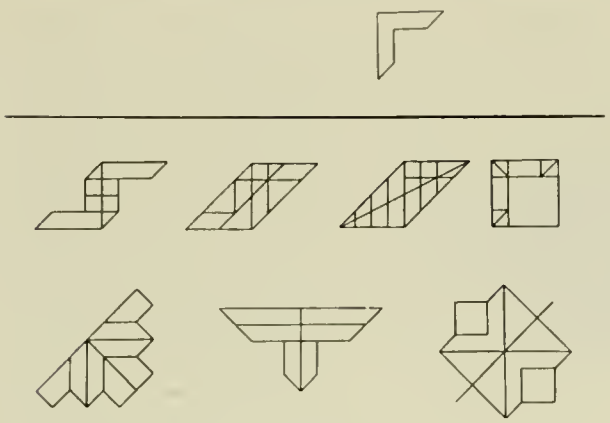


FIG. 14. Hidden-figure test (sample page), modified after Gottschaldt (164, 165). The subject is required to find the figure at the *top* within each of the *lower* (*embedding*) *figures*. [From Teuber & Weinstein (479).]

the perceptual analysis of such patterns (161, 386, 479). However, while field defects are sufficient to produce such a deficit, they are not necessary. Injuries in any lobe of the brain, in either or both hemispheres, lead to significant loss on this task (fig. 15; 479). Neither does it seem necessary that there be other symptoms of cerebral lesion, such as somatosensory or motor changes (see fig. 16), since following brain injury subjects with or without such symptoms perform equally poorly as compared with normal controls. Only aphasic patients, as a group, can be shown to fall significantly below the others with brain injury (see, again, fig. 16), who in turn are surpassed significantly by the controls.[14]

Perceptual changes after cerebral lesions in man thus range from those that are most specific (scotomata) to those that are general, or nonlocalizable. Which one of these alterations appears seems to depend on the nature and level of the task employed. Such findings recall the belief of Flourens (127) who assigned to all major sectors of the forebrain an *action commune*, in addition to their *action propre*. If one considers the wide scope of perceptual selectivity in higher forms, one can perhaps understand its dependence on such common action of the hemispheres and its nonspecific decline after brain injury in man.

Analogous hierarchical findings can be obtained for man's somatosensory systems. Here, alterations in basic sensory thresholds after lesion of the somatosensory projection system correspond to the scotomata in the visual sphere. By their very nature, these deficits might be expected to interfere with the perception of what are traditionally known as 'higher' or complex aspects of objects presented through the sense of touch. However, the classical concept of 'astereognosis' (i.e. agnosia for touch) suggests that recognition of object qualities can be impaired in the absence of any 'primary' or 'elementary' deficit in that modality.

Difficulties in tactile perception, then, could reflect either a mere consequence of sensory alterations (such as changes in thresholds) or a separate higher-

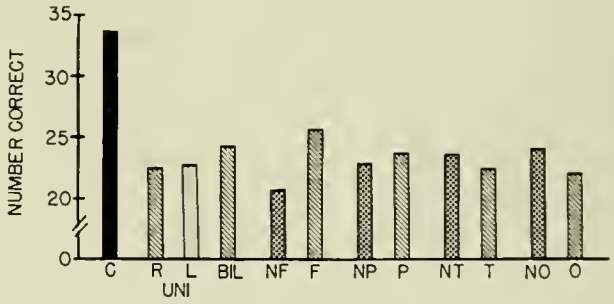



FIG. 15. Average number of hidden figures (see fig. 14) correctly traced by normal adults (controls, *C*) and by subjects with brain injury, grouped according to location of lesion: *L*, left unilateral lesion; *R*, right unilateral lesion; *F*, *P*, *T*, *O*, frontal, parietal, temporal and occipital, respectively; *NF*, *NP*, *NT*, *NO*, nonfrontal, nonparietal, etc. [From Teuber & Weinstein (479).]

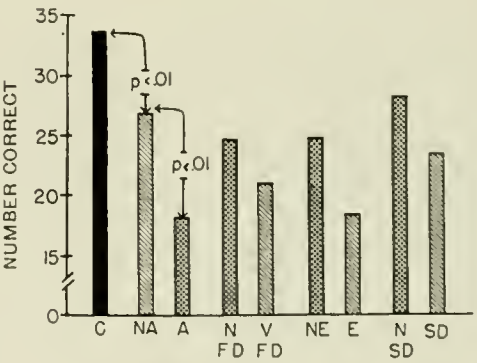



FIG. 16. Average number of hidden figures (see figs. 14, 15) traced correctly by controls (*C*) and by subjects with brain injury, grouped according to presence or absence of aphasia (*A*), visual field defect (*VFD*), epilepsy (*E*) and somatosensory defect (*SD*). Absence of a given defect is indicated by *N*. [From Teuber & Weinstein (479).]

[14] This nonspecific deficit on hidden-figure tasks cannot be interpreted as some form of generalized intellectual decline, since intelligence [at least as defined by routine tests, e.g. Weinstein & Teuber (528) and Teuber (467)] turned out to be unimpaired in all but a few members of the groups to whom the hidden figures were presented.

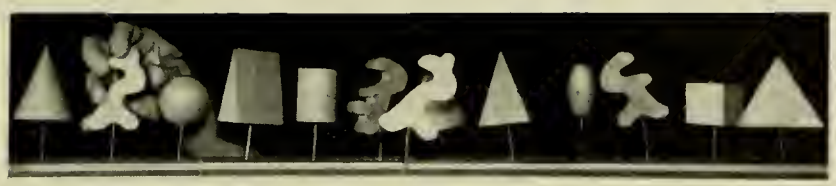


FIG. 17. Test for recognition of solid forms. Subject palpates sample form (*front*), and attempts to find the identical form within the array (*back*). A black curtain screens the test patterns from subject's view. [From Teuber (467), based on Ghent *et al.* (149).]

level disturbance, independent of sensory status. Neither of these possible interpretations seems to fit the recent observations in man following brain injury. On a variety of tests of object recognition (149, 417, 527), subjects palpate a given object with one hand, and then try to find a replica of that object with the other hand (see fig. 17). On a number of these tests, men with sensory impairment of one hand show impaired performance of object discrimination in both hands, not only the one opposite their brain injury, but also in the ipsilateral hand which had seemed intact on all primary tests of sensory function (see fig. 18).

This unexpected finding shows that discrimination deficits are associated with more basic sensory defects, but transcend these basic defects by involving seemingly unimpaired parts of the patient's body. These observations are strikingly parallel to those made on visual functions after lesions of the central visual pathways; there, too, specific defects (scotoma) are restricted to certain regions, while the more subtle deficits, such as lowered flicker-fusion, go beyond the area of primary defect and involve the entire visual field.

In addition, we must recall that all groups of patients tend to show disturbances on the hidden-figure tasks already discussed, so that somatosensory changes are sufficient but not necessary for this general perceptual deficit which is found after cerebral lesion in man. The data available for infrahuman forms with subtotal lesions within or beyond the primary projection systems are analogous in certain respects.

EFFECTS OF SUBTOTAL LESIONS IN ANIMALS BELOW MAN. The most general consequence of subtotal removal of primary projection fields in rodents, carnivores or subhuman primates is again the resiliency of shape perception as such. Failure to find some of the subtle associated changes in residual function may be due to the absence of tasks that would be sufficiently sensitive, rather than to an absence of the deficits. The resiliency of form perception has been shown, for instance, in rats with

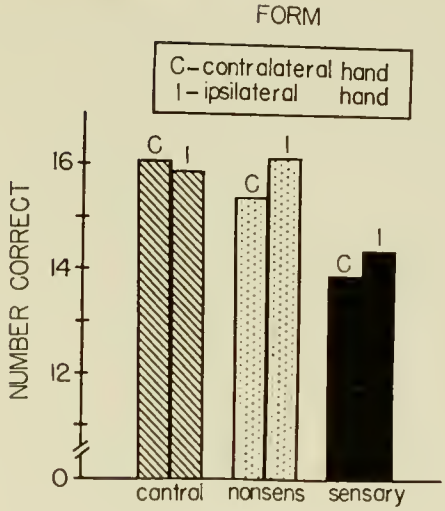



FIG. 18. Results of form recognition task (see fig. 17). In the control group (without brain injury), *C* and *I* hands are left and right, respectively. Note the reduction in score for both hands in the group with sensory defect (as defined by elementary sensory tests), even though the elementary defect is restricted to one hand. The group with brain injury without these elementary sensory defects (nonsensory) does not differ from the controls. [From Teuber (467), based on Ghent *et al.* (149).]

large striate cortex lesions, leaving only $^1/_{60}$ of the striate cortex intact (302). Similar observations on rapid recovery of pattern vision after extensive but subtotal ablations of striate cortex have been made in monkeys [see Klüver (260), Harlow (180) and Setlage (420, 421)].

In Hebb's theory (188) of pattern vision, excitation within the primary visual cortex (area 17) has to be transmitted to surrounding prestriate regions for perception to take place. The resiliency of pattern vision in small islands of preserved cortex casts doubts on these notions, unless one assumes that the interaction between striate and prestriate systems employs thalamic or other subcortical connections.

Even more embarrassing to theory, however, are the negative results after extensive removal of prestriate cortex in the monkey (115, 306). Traditional doctrine has always assigned crucial functions to the areas of cortex which surround primary projection

fields. The prestriate region was considered 'visuopsychic,' the midparietal 'sensoripsychic,' and certain temporal lobe structures (lateral and inferior to primary auditory fields) were considered 'audiopsychic.' In every instance the assumption was that elementary sensory processes took place in the projection fields, and higher 'apperceptive' or 'associative' perceptual processes, in the adjacent psychic field (125, 362). Destruction of the latter was believed to produce agnosia—a disorder of recognition of patterns presented to a given sensory modality in the absence of more elementary sensory disturbances sufficient to account for the observed difficulties with object recognition. This traditional view is difficult to maintain in the case of the rat or the monkey, although one might raise the question of whether agnosia, in the classic sense (132, 362), should ever be expected to occur in subhuman forms. As we have seen, however, the evidence regarding agnosia in man is far from clear.

The data in lower forms, particularly the rat, prompted Lashley (305) to propose that a primary projection area, such as the visual cortex, might be autonomous. No part of the cerebral hemisphere, except the visual cortex itself, seemed to him essential for establishing perceptual reactions, including those of the most complex type of which the normal animal was capable (304, 305). This view, however, is difficult to reconcile with the impression that any major cortical region mediates both its own specific and some more general activity, an impression that derives just as much from Lashley's own maze-running studies (300) in the rodent and from the more recent work on reaction to complex perceptual tasks in man (467).

Observations which detract somewhat from the concept of complete autonomy of the primary visual area have been obtained by Sperry (439) and Myers (357). The observations are the most recent outcome of a series of studies on effects in cats of combined sagittal section of the optic chiasm and the corpus callosum. Such 'split-brain' preparations (see fig. 19) can be trained to make visual discriminations with one eye, but they fail to transfer to the other (untrained) eye under most conditions of training and testing.[15] In such animals one hemisphere can be left intact, while extensive lesions are made in the other; instead of making the usual ablation in a small area suspected to be critical, a large complementary lesion can be made, leaving only the critical area intact. If the visual cortex in one hemisphere is isolated in this manner (see fig. 19A), nearly all previously learned visual discriminations with the eye on that side are lost. The simplest discriminations (horizontal vs. vertical stripes), however, may be occasionally preserved; if lost, they can be relearned. Preoperatively learned discriminations between circle and cross can also be relearned (though with deficit),

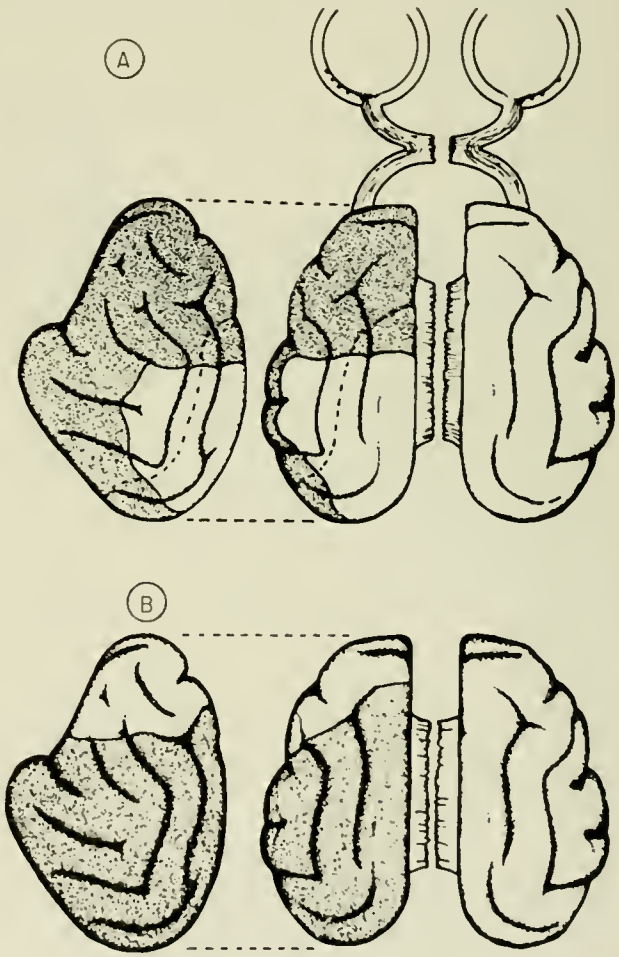



FIG. 19. Schematic views of experimental lesions in 'split-brain' cats. *Top*, complete sagittal section of optic chiasm and of corpus callosum, combined with partial decortication of left hemisphere, leaving the visual cortex as an island of spared tissue. *Bottom*, callosal section combined with another partial hemidecortication, leaving an island of spared sensorimotor cortex. [From Sperry (439); see also Myers (357).]

[15] It must be noted that this failure of transfer from hemisphere to hemisphere is again a function of the 'level' of the task employed. If the 'split-brain' animal is required to learn a simple visual discrimination (vertical vs. horizontal stripes) in order to avoid a painful shock, the information does transfer from one eye to the other.

but a preoperative discrimination between upright and inverted V's is permanently lost. The animals show impairment in everyday situations; they bump into objects in a strange room and have trouble finding food held in front of the affected eye. None of these difficulties is found on testing the other eye.

It is important to note that the impairment of visual discrimination increases with increasing ablation from supposedly nonvisual areas. When the removal is done in two stages, and the first includes the temporal lobe and all cortex adjacent to the visual island, the deficit is present but less severe. If one then removes the frontal region, the impairment becomes approximately as severe as if the total removal were made in one single stage. For instance, it is only after the second removal that the animals show the permanent inability to discriminate upright and inverted V's. Such results suggest that the most anterior regions play some role in visual performance.

Curiously, the results are different for somesthetic discrimination. If an island consisting of sensorimotor cortex is produced in a 'split-brain' cat (by decorticating the rest of one hemisphere, as shown in fig. 19*B*), tactile discriminations trained in the corresponding (i.e. opposite) forepaw are retained; they are permanently lost when the island of cortex is removed. The greater functional efficiency of the isolated somatic cortex, as compared with isolated visual cortex in the cat, might suggest a different mode of organization in these two sense modalities. However, it may be important, as Sperry himself points out (439), that the isolated somatic cortex does include a 'motor' area, while the isolated visual cortex does not.

### *Isolation Studies*

The recent studies by Sperry (439) employ ablation techniques to achieve various degrees of anatomical isolation of primary receptor fields within the neocortex. The effects on function are actually not as drastic as those of another technique of isolation, that of depriving an intact organism, early or later in life, of normally patterned sensory input.

PATTERN VISION AFTER REMOVAL OF CONGENITAL CATARACTS. In man, such sensory deprivation is often thought to result from congenital cataracts which prevent pattern vision until the cataracts are surgically removed (511). The problem was posed by Molyneux (351) and discussed by Berkeley (38) and Diderot (105). Would a man, born blind, whose sight has been restored, manage to identify, visually, patterns familiar to him from his earlier tactual experience? The majority of clinical reports on such cases has given a negative answer [see von Senden (511)]. The formerly blind patients have to go through prolonged periods of acquisition of pattern perception. They may be able to distinguish colors before they can discriminate shapes. They distinguish a square from a hexagon by laborious and often erroneous counting of corners, confuse a rooster with a horse (because both have tails), or call a fish a camel (because they confuse the dorsal fin of the fish with a camel's hump) (524).

These reports may indeed mean what von Senden (511), their compiler, thought they meant, that normal shape perception is acquired through early learning and that early isolation from patterned visual stimuli retards or prevents the necessary learning to perceive. Yet there are serious ambiguities in this clinical evidence. The case reports are rarely adequate [see Michael Wertheimer's critique (538) of von Senden's material], and there is the possibility of other lesions in patients with cataracts which makes the interpretation doubtful.

EFFECTS OF EARLY VISUAL DEPRIVATION ON SHAPE PERCEPTION IN SUBHUMAN SPECIES. It is for this reason that a number of recent experimental studies have been done, primarily on Hebb's suggestion (188), employing the paradigm of early visual deprivation in lower forms; in birds (429, 430), rats (187), cats (401–403) and chimpanzees (88, 363, 400). Paradoxically, Hebb himself had shown earlier (187) that rats reared in darkness were capable of practically normal visual pattern discriminations when first brought into light. In birds, such as ring doves (429, 430), rearing with translucent goggles (eliminating patterned light stimulation) results in some retardation of shape discrimination learning when the goggles are removed. However, the deficit is not great. In fact, the animals can be given their first visual discrimination training with one eye; when tested for 'transfer' of this learned discrimination to the other (untrained) eye, they show some transfer (since they need significantly fewer trials for the second eye). An extreme form of Hebb's empiricist theory would predict no interocular transfer for these visually naive animals, while extreme forms of Gestalt theory

would predict 100 per cent transfer.[16] Apparently the visually deprived birds choose to place themselves midway between these theoretical positions.

The most serious effects of early visual deprivation, however, have been reported for cats (401–403) and chimpanzees (88, 363, 400). The earliest accounts of visual deficits in the latter [two animals studied by Riesen (400)] should perhaps be disregarded, since the optic atrophy induced after 16 mo. in darkness was severe and progressed in one of the two cases to complete blindness. Later studies (403), however, employed diffuse light as a condition of early rearing, or a combination of darkness and diffuse light, which was thought to prevent any atrophy of disuse. These animals were at first unable to distinguish such simple visual patterns as horizontally vs. vertically striped fields, they failed to recognize their feeding bottle until it touched some part of their body, and they showed general neglect of their visual environment.

ALTERNATIVE INTERPRETATIONS. Still, the interpretation of these fascinating experiments is problematic. There are at least three other mechanisms besides the one usually advanced that might account for the visual difficulties after early visual deprivation: atrophy of structure, suppression of function, or general behavioral impairment.

*a*) Some atrophy of disuse may occur in spite of the precautions taken. Brattgård (59) has found that rabbits reared in darkness for 10 weeks from birth showed complete lack of the pentose nucleoprotein fraction in their retinal ganglion cells. Animals brought out into light afterward did not develop pentose nucleoprotein at the same rate as did controls. In kittens reared in the dark, Zetterstrom (558) noted that the electroretinogram (ERG) did not appear until the third week from birth; normally reared kittens show some ERG activity by the end of the first week. Finally, in the most detailed histologic study of this question to date, Weiskrantz (529) has demonstrated significant losses of fibers (especially the so-called Müller fibers) in the neuroretinae of kittens reared under the same conditions as those employed by Riesen *et al.* (403). He points out, rightly, that these findings do not rule out the hypothesis that perceptual learning must occur as a necessary part of development. However, the evidence of atrophy diminishes the value of early sensory deprivation as a test of this hypothesis. It may be convenient, as Weiskrantz notes (529), for psychological theory that deprivation should produce changes limited to higher neural structures, but perhaps it is less convenient "for the nervous system itself to make such a distinction."

*b*) Another potentially complicating factor is suppression of function in the deprived sensory modality. Such a process is perhaps not as hypothetical as it was prior to the demonstrations of suppression of afferent visual or tactile input upon midbrain reticular stimulation [see Granit (168)], or the transient changes in evoked potentials at lower levels of the cat auditory system during 'distraction' [see Hernández-Peón *et al.* (204)], or during conditioning [see Galambos *et al.* (140)]. In man, suppression is said to play a role in the curious impairment of pattern vision in the deviated eye in cases of unilateral squint. This strabismic amblyopia is often called '*ex anopsia*,' as if disuse were the cause of the perceptual deficit. For the neoempiricist, however, the squinted eye does not 'get amblyopic,' but 'stays amblyopic,' i.e. it does not build up those normal relations between eye movements and patterned visual stimuli which (for Hebb) are prerequisites for acquisition of shape perception.

Studies of basic visual thresholds (such as dark adaptation, spectral sensitivity and absolute brightness threshold) reveal essentially normal function in such squinting eyes in which form perception is lacking (514). The condition has therefore been interpreted by Wald & Burian (514) as a selective impairment of a 'higher' level of vision, i.e. of pattern perception, since, in their opinion, the 'entire apparatus of light perception' remains intact in the affected eye. More recently, however, Feinberg (123) has demonstrated that there are, after all, demonstrable changes in more elementary visual functions, e.g. a drastic

[16] Normally reared birds show 100 per cent interocular transfer under comparable conditions, i.e. one eye knows what the other has been taught, at least as long as the patterns are presented in the lower part of the visual fields (265, 266, 317–319). A negative result (failure of interocular transfer for a color discrimination in the pigeon) has been reported by Beritov & Chichinadze (37). Interocular transfer is present but less consistent in fish (341, 440). In the goldfish, for instance, transfer from eye to eye may fail if the index of transfer is an overt avoidance response to electric shock (341). The animal is warned prior to the onset of the shock by the presentation of a visual pattern (a vertically striped field) to one eye. After the animal has learned to make a forward movement (avoiding the shock) each time the pattern appears, the second (untrained) eye is tested under the same conditions. The avoidance response fails, but the animal does show a transfer in terms of a conditioned change in heart rate. Anthropomorphically speaking, one might say that the pattern does look 'threatening' to the untrained eye, but the animal does not know what to do about the threat.

reduction of flicker-fusion, in such amblyopic eyes. These results show again that subtle alterations in perceptual function may be elicited when multiple or recurrent stimulation (permitting stimulus interaction) is employed (465, 469).[17]

Another defect in strabismic amblyopia which suggests suppression had been discovered much earlier by Harms (181). The pupillomotor effect of light cast suddenly on the fovea of such an amblyopic eye is distinctly less than that in the normal eye; more curiously, the diminished pupillary constriction occurs alternately in patients with alternating squint; the pupil of the momentarily deviated eye responds less. Extending these observations to normal eyes, Bárány & Halldén (18) were able to show that the same suppression of pupillary response occurs during retinal rivalry (induced by presenting conflicting contours to the two eyes of normal observers). These results again suggest that retinal suppression takes its effect all the way 'downstream' in the visual system.

*c*) A final difficulty in the interpretation of deprivation studies is the possible general (nonspecific) retardation induced by such drastic changes in an animal's early environment. Hebb himself (188) has argued forcefully for the role of impoverished environments during infancy in producing generalized emotional and intellectual deficits in later life. A number of studies stimulated by him have tended to confirm this view [e.g. those of Forgays & Forgays (129), Forgus (130), Hymovitch (233) and Thompson & Heron (483)]. In line with these experiments are the studies by Axelrod (16) which proved that blindness of early onset in children produced subtle but consistent deficits on nonvisual (auditory and tactile) tasks; there also were abnormal difficulties of intermodal transfer (from tactile tasks to their auditory analogues, and conversely). These deficits were less marked or absent in children who had lost their sight later in life. Some care had been taken in this study to provide perceptual tasks which were not spatial in any obvious way. Earlier work on congenitally blind children had stressed a possible impairment on tasks involving the manipulation of objects in space (109).

The discussion of deprivation experiments, and of the related results of recombination studies (e.g. perception with inverted visual fields), will be resumed after reviewing spatial organization, movement perception and perceptual constancies.

## DEPTH, DISTANCE AND OTHER ASPECTS OF SPATIAL LOCALIZATION

As we shall see, the problem of depth perception is intimately connected with that of motion perception and with the perceiver's ability to apprehend a rigid environment during self-induced movement. Nevertheless, the traditional approach to depth perception reflects what has been called the 'geometric fallacy' (154). It is assumed that the observer be motionless, that his eyes receive passively the images of objects located at various distances, and that the question should be how a two-dimensional array (the retinal 'image') could carry enough information to constitute a three-dimensional scene.

### *The Traditional Approach (Depth from Clues) and Its Alternative (Depth from Gradients)*

The traditional answer has been that the two-dimensional retinal image is somehow reinterpreted by means of clues or cues for depth. Here the word 'clue' bears a frankly intellectualist connotation, while 'cues of depth' denote individual mechanisms called onto the stage on various occasions, often unbeknown to the perceiver. These clues or cues for depth are usually divided into those available to a one-eyed observer (monocular cues) and those dependent on binocular parallax.

MONOCULAR CLUES. Monocular determinants include relative size of 'familiar' objects (the farther, the smaller), relative clearness, shading [see, for example, von Fieandt (497)], and interposition in which one contour is partly obliterated by another in front of it [see Ratoosh (395) for a mathematical formulation]. All these cues are clearly derived from the art of perspective painting, an invention of the Renaissance, where a stationary two-dimensional picture is so arranged as to give the illusion of three-dimensionality. It is thus not without reason that Leonardo da Vinci in his *Paragone*, *Trat.* 35, cited by Richter (316), insisted on calling painting a science ("which shows . . . wide landscapes with distant horizons on a flat

[17] Wald & Burian (514) invoke the results of occipital lobectomy in monkeys as an evolutionary analogue for their separation of lower from higher visual functions, since such monkeys "lose virtually all capacity for pattern vision while retaining sensitivity to light, brightness perception, and visual space localization." However, Klüver (261) has demonstrated that residual light perception in the monkey consists of a response to total luminous flux. This mode of response has never been observed in the foveal regions of an intact animal; it is to be distinguished from brightness discrimination in the usual sense (see below, pp.1652–1653).

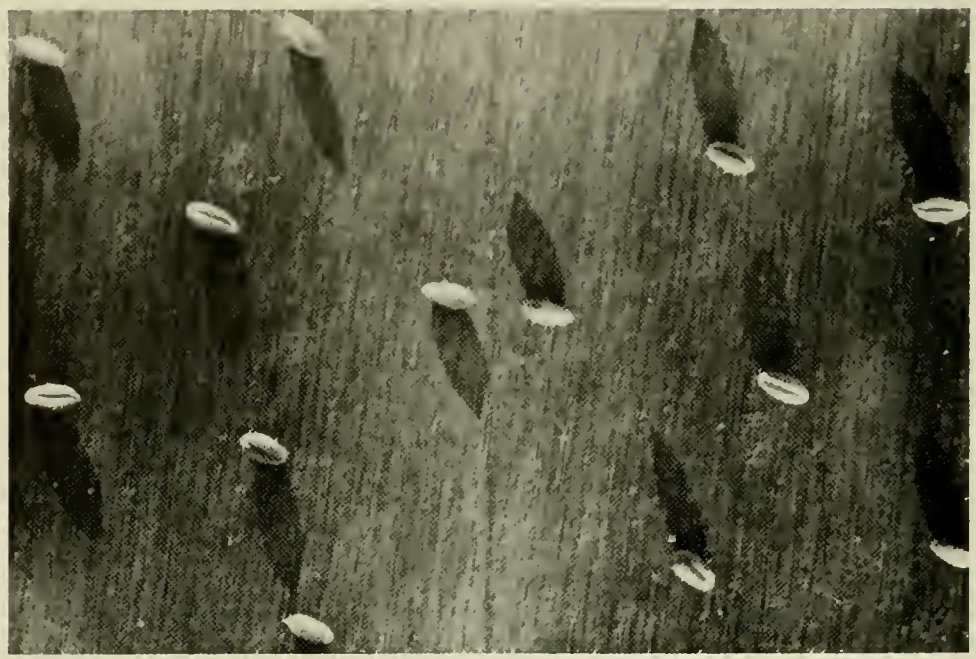


FIG. 20. Test photographs presented to chicks reared in light coming from below their cage. Such birds peck predominantly at the *right section* of the photograph. Control chicks reared in light coming from above their cage peck at the *left section* of the photograph. The two sections were prepared from the same negative. [From Hess (211).]

surface") and that he introduced numerous analytic experiments into the study of depth perception.

It is in fact possible to isolate individual cues or to provide conflicting ones, but it is equally clear that cues are not additive in any simple fashion, but interact as parameters of depth. Moreover, the evidence already presented (in the discussion of pattern vision) indicates that a positive depth impression (without definable distance) is obtained in a diffusely illuminated sphere (without visible microstructure—the *Ganzfeld*), and while considerable practice is needed in man for adequate estimates of distances, depth as such might well be an immediately given aspect of a visual scene, just as it is characteristic of auditory and tactile-kinesthetic space.

Thus, chicks show visually guided pecking responses to grain which have considerable accuracy immediately after hatching [see Hess (211)]. The response can be molded, during the first month of their lives, by providing unusual cues—e.g. by illuminating their cage from below (see fig. 20). Chicks so reared will peck at photographs of grain in which the shadows are above rather than below the image of the grain. Still, the confusion of photographs of grain with real grain attests to the compelling nature of the pictorial representation. In man too, compelling depth can be obtained by reproducing photographs of a scene on a large screen (diminishing thereby the opportunity for comparison with 'real' tridimensional objects), or by looking at a small photograph under a high-power wide-angle lens (413).

The depth effects obtained from paintings and photographs, in the absence of binocular disparity, are particularly important because they show that two other traditional 'cues' of depth—those of accommodation and convergence—are far from indispensable. Attempts at defining the role of these monocular cues [clearly invoked already by Berkeley (38) in 1709], can furnish particularly striking examples for the artificiality of univariate experimentation: the effort at isolating a single set of 'proprioceptive cues' introduces ambiguity into perceptual situations which, under normal conditions, are always multidetermined [see Woodworth & Schlosberg (549, pp. 475–480) for review and critique]. Undoubtedly, both accommodation and convergence may furnish information about relative distance (53), but this information serves only over a rather short range of distances (probably

not much beyond 6 m from the eyes); it may be more important in enhancing accuracy of distance judgments than in providing us with elementary impressions of depth. The role of these mechanisms in aiding perceptual constancy, especially of size, is another matter (see below).

DEPTH FROM GRADIENTS. A refreshingly new approach to the study of depth perception has been introduced by Gibson (154). Rejecting the emphasis on manifold but separate clues or cues, Gibson has pointed out that a convincing two-dimensional picture of a surface slanting into the third dimension is obtained by presenting 'gradients of texture'; an array of patterns (e.g. circles) set up in rows and columns will give the impression of a receding slanting plane, if successive rows, from the bottom of the picture to the top, diminish in size and increase in density. The same effect can be obtained with converging lines, as shown in figure 21. Gibson believes that such texture gradients provide a psychophysical correlate of monocularly obtained depth and that many of the traditional cues can be subsumed under this gradient notion.

These gradients in a scene become even more effective when the observer (or his eyes) move relative to the environment. As Gibson points out, there is more than classical motion parallax involved in the resulting transformations. During the landing glide of an aircraft, for instance, complex but characteristic flow patterns deform the ground below, and the clouded sky above, in a continuous sequence of 'perspective transformations.' The point on the landing strip toward which the pilot moves forms the center of an expanding pattern; everything around it moves radially away from this center (fig. 22).

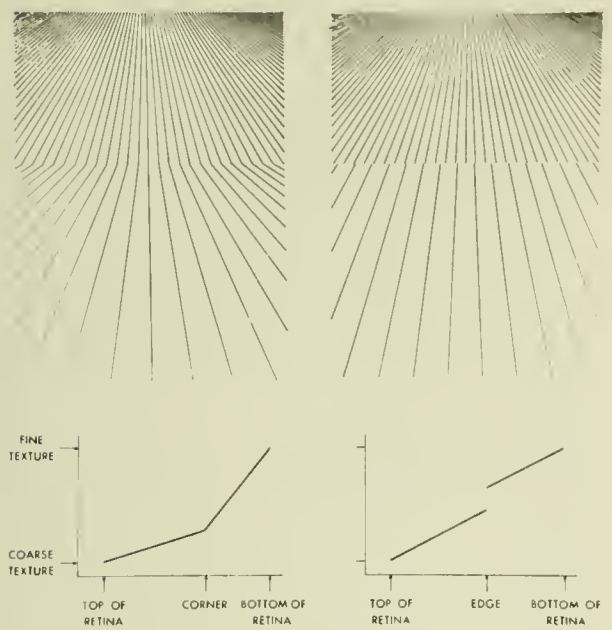



FIG. 21. Depth from gradients. *Left*, a change of gradient corresponding to a corner; *right*, a jump between two gradients corresponding to an edge. [From Gibson (154).]

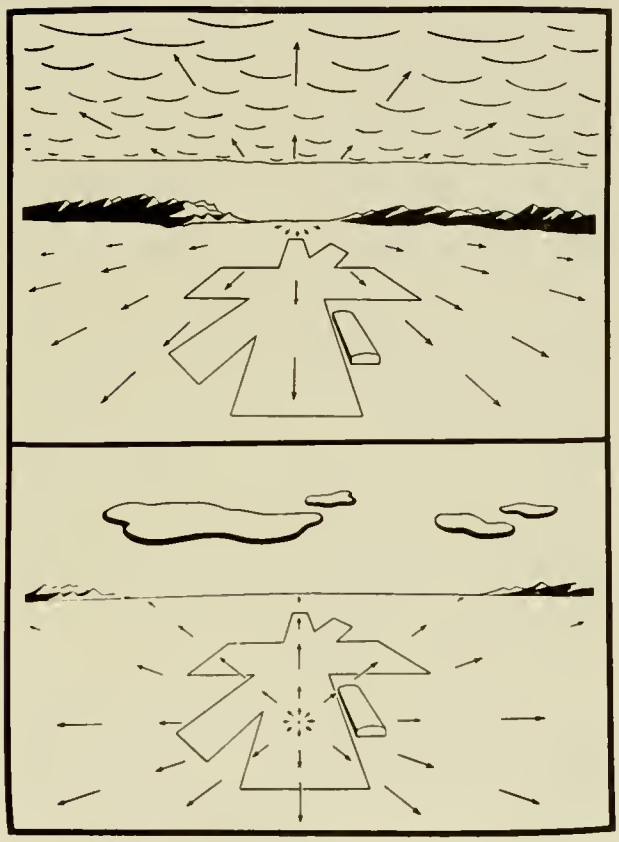


FIG. 22. Flow patterns (continuous perspective transformations) in the visual field of a pilot in level flight (*above*) and during a landing glide (*below*). [From Gibson (154).]

In addition, Gibson suggests that there is usually enough in the stimulus pattern, at least in natural surroundings, to enable a perceiving organism to distinguish his own movement through space from the motion of objects in the scene relative to the perceiver; self-movement results in characteristic perspective transformations of the entire scene (156). It is for that very reason that movement of the entire scene, or most of it, relative to the observer, tends to be ambiguous; the observer readily believes himself to be moving, in direct confirmation of Duncker's experimental results (110) on induced motion (that

the enclosed object is seen as carrier of motion, rather than its surround).

KINETIC DEPTH EFFECTS. A striking instance of the close connection between depth and motion are the kinetic depth effects (346, 519); a two-dimensional shadow on a translucent screen may give the impression of three-dimensionality if the shadow-casting object behind the screen (e.g. a wire triangle) is slowly rotated. To Wallach and his colleagues (520) this effect is indicative of the influence of memory of past impressions on present experience—a revival of the classical distinction of sensation and perception. In fact every instantaneous impression of the shadow does look flat, but their succession provides, in the terminology of the Gibsons (157), a continuous series of perspective transformations which can form an adequate stimulus correlate of both depth and motion. They point out, further, that the face of a solid object is usually given "not as a form, but as a unique family of transformations" (157).

These kinetic depth effects thus furnish particularly convincing instances of the general rule that sequential as well as instantaneous patterns are the important bases of perception. It is no accident that constancy of shape is very much enhanced when objects are slowly rotated, as in the experiments by Langdon (299). Perceptions of shape as well as depth and motion are normally dependent on sets of transformations, rather than instantaneous impressions of static patterns presented to an immobile observer.

BINOCULAR PARALLAX. If all this is true, then the most famous of all single 'cues' of depth—the one resulting from binocular parallax—is likewise demoted from its primary to an auxiliary role. Effects of disparity, in binocular vision, may be merely a special form of the gradients which Gibson has described (154). Binocular fixation yields two slightly differing views of a single object; the difference increases as the object approaches the eyes. To the earlier investigators of depth perception, it was the triangulation thus produced that seemed to be, if not the only, then the most powerful source of perceived depth (38, 53, 154). This belief was buttressed by Wheatstone's discovery in 1833 (540) of the stereoscope which proved that horizontal disparity of two flat patterns presented one to each eye could act as a single determinant of depth. But reliance on the stereoscope as paradigm of depth makes one miss half of the problem. It might seem that all we need to understand is how the nervous system combines the two 'retinal images' into a single view. Yet for a real tridimensional scene, geometry of binocular vision requires that the singleness of vision be restricted to the points that are fixated; all objects lying closer or farther than the fixation point should appear double.

Since the time of Aguilonius (3), the term 'horopter' has been in use to describe the set of all points that ought to be perceived as single in the monocular field of vision. The corollary of the horopter notion is binocular diplopia for all points lying outside this horopter surface. The normal binocular observer, however, has consistently ignored these geometric constructions; he sees a tridimensional scene in which objects are fused throughout. Does he do this by 'suppressing' his double images? Some investigators in the nineteenth century thought he did, but Hering pointed out (199) that by suppressing his double images, the perceiver would lose valuable information about depth. Again for geometric reasons, all objects lying closer than the fixated one should appear in double images that are crossed, while objects beyond the fixated ones should appear as uncrossed double images. But this observation raises only a further paradox; since the perceiver cannot distinguish which eye is obtaining which view, how can he tell near from far, i.e. crossed from uncrossed disparity?

It seems to us that all these paradoxes arise only in an 'image theory' of perception. They disappear if one considers instead the serial patterns of stimulation with which binocular depth perception is correlated. There is a gradient of increasing disparity which stretches from any fixated object toward the horizon, and there is a converse gradient which decreases from maximal disparity near the eyes towards the fixated object where it becomes minimal [see Gibson (154, pp. 100–108)]. A stepwise change in such disparity gradients yields an edge, just as it does on monocular viewing of gradients of texture (see above, fig. 21). These discontinuities furnish the 'empty spaces' that are seen in such compelling fashion between overlapping objects appearing at different depths in a stereoscope.

Consider the stereograms in the upper part of figure 23. When combined into a single view in a stereoscope, the arrangement on top gives the impression of a surface like a wall which slants to the right, if the horizontal gradient of disparity increases to the right. Interchanging right and left images yields a corresponding slant to the left. A gradient of disparity that runs vertically up or down (as the one obtained on combining the two lower stereograms in the bottom half of fig. 23) provides a slant such as that

of a floor or ceiling (154). The impression of a floor slanting up is gained when the left and right views are combined as shown; when they are interchanged, one obtains the impression of a downward slant (like a ceiling). The approach to binocular vision based on disparity gradients makes it possible to understand yet another seeming anomaly of depth perception. In the stereoscope, it is possible to obtain some binocular depth with patterns or settings that are too disparate for fusion. This observation has been reconfirmed by von Tschermak-Seysenegg (513) and Ogle (365).[18]

ACUITY OF BINOCULAR DEPTH PERCEPTION. If binocular stereopsis is not a principal source of depth, it nevertheless adds precision. The degree of this precision is astonishing. In defining its limits, one needs to determine the minimal difference in depth that can be mediated by binocular parallax. Thus, given a distance, $D$, along the line of regard, what is the minimal additional distance, $\Delta D$, that can be perceived? The question has been investigated since von Helmholtz (501) with his famous three-needle experiment and with many variations, including the (rather crude) screening device for assessing binocular stereopsis called the Howard-Dolman apparatus. With this device, the observer on repeated trials aligns two movable vertical black rods until they seem equidistant from himself. Tactile-kinesthetic

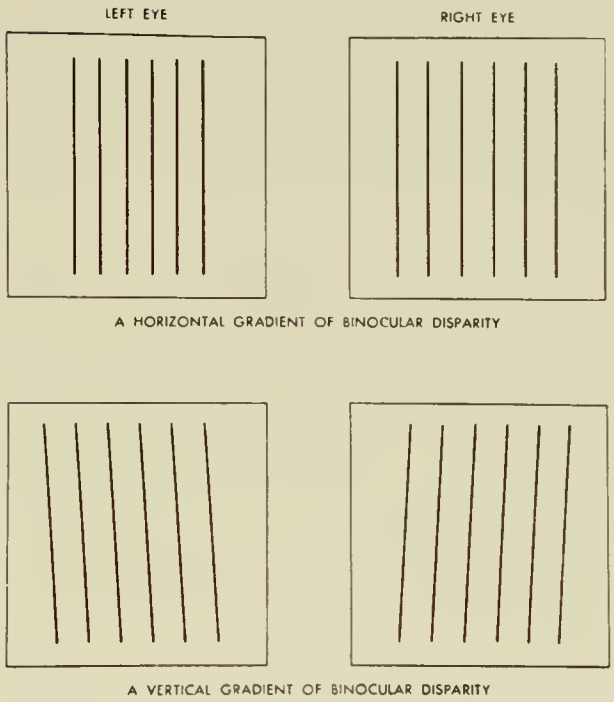



FIG. 23. Pairs of stereograms based on gradients of binocular disparity corresponding to fundamental types of slanting surfaces. [From Gibson (154).]

information is eliminated by attaching the rods to an endless loop which the observer manipulates, and accommodation and convergence are minimized by keeping the apparatus at a distance of at least 6 m. Under such conditions the minimal disparity utilized (by the 'best' observers) can be as low as 2 sec. of arc.[19] Such values of $\Delta D$ vary systematically with illumination and absolute distance of the rods, with their thickness and angular separation, and other factors (166). Values for minimal disparity that are nearly as low (i.e. 5 to 10 sec. of arc) can be obtained on stereoscopes by using, for example, the Keystone series of stereograms where disparity is systematically increased from pair to pair throughout the series of test cards (549). The acuteness of binocular stereopsis can be utilized in detecting slight discrepancies between patterns; the views of a genuine and a

[18] The approach to binocular depth perception which invokes gradients of disparity makes it understandable that altering the disparity between monocular stimulus patterns in a particular dimension should radically alter the appearance of the visual scene. The aniseikonic glasses (meridional size lenses), studied by Ogle (364), Burian (77) and Ames (6), have such effects in commonplace environments. "Objects not only appear at distances other than those for which the eyes are accommodated and converged, but they appear to be of unexpected sizes and shapes which do not correspond to the 'geometrical dimensions' of the stimulus patterns and have unexpected apparent motion" (6). A special, and much simpler form of 'false depth' in binocular vision is induced by placing a filter of neutral density before one eye while viewing a pendulum bob which swings in the viewer's frontal plane. The pendulum then seems to describe an elliptical path (with axes parallel to the floor). Pulfrich (390) who discovered the effect attributed it to the greater latency of visual impressions in the less illuminated eye, yielding a 'surplus' binocular disparity [see also Liang & Piéron (322) and Lit (326)]. If the pendulum is made to swing vertically through the viewer's binocular field, the effect disappears (as it should if it were due to a form of binocular parallax), but intermediate trajectories do not yield the depth values predicted by the simple parallax theory, and there are observers who have obtained the Pulfrich effect when each eye had monocular stimulation in succession (253).

[19] If Gibson's approach to depth perception is correct, it will be understandable that measurements of this type (e.g. in the Howard-Dolman apparatus) are poor predictors of depth perception in real-life situations, such as in piloting a plane. Only frank diplopia may be a handicap there, although it is true that even mild anoxia can convert a latent into a manifest strabismus with resulting binocular diplopia.

forged bank note, combined under a stereoscope, will make the deviant features stand out by producing an impression of relief in the combined view. There are similar applications of stereoscopy for discovering camouflaged features in aerial photographs taken at slightly different angles.

THE LOCUS OF BINOCULAR FUSION. The question of how and where the activities of the two retinae interact in the nervous system is only a special form of the problem of patterning. Perceptions mediated by different portions of a single eye, or a tactile surface, raise actually the same unresolved issues. Yet physiologists have long regarded binocular fusion as a more accessible problem, even though the answers differed. For Kepler in 1611 (255), 'images' of the two eyes were 'projected' by the mind to the single object on which the eyes converged. For Porta, in 1591 (387) there was no problem because the two eyes alternated, he believed, in continual rivalry. Newton in 1704 (361) rejected both views and invoked instead the decussation of the optic nerves and their ultimate convergence at higher levels in the nervous system as the structural basis of binocular fusion. There the problem remains.

Anatomically, the optic tract fibers in mammals (carrying impulses from ipsilateral and contralateral eyes, respectively) terminate at separate layers of the lateral geniculate body. This segregation may continue at the striate cortex. For man and monkey, it has been proposed by Kleist (257) that the ipsilateral elements of the optic radiation end in lamina IVa of the striate cortex, and the (more numerous) contralateral elements in lamina IVc. The intervening lamina IVb—the stripe of Gennari—has been claimed to represent a binocular mixing zone (257). [The arrangement was considered by Bárány in 1924 (19) but rejected in favor of a postulated ending of ipsilateral and contralateral elements at different depths of IVc, with the stripe of Gennari again acting as a mixing zone.] These attributions remain as conjectural as Wilbrand's theory (541) which postulated that ipsilateral and contralateral elements were placed at the same depths within the visual cortex in the manner of black and white squares on a checkerboard. Microelectrode studies of cortical neurons apparently reveal a considerable number of units responding to both eyes (224); recording from different depths may show whether there is also some laminar segregation of monocular elements or not. Electrotonic interaction between lamina has been proved for the lateral geniculate by Bishop & Davis (45) so that anatomic separation of layers would not preclude the interaction of ipsilateral and contralateral lamina upon simultaneous or closely successive stimulation. Binocular flicker fusion differs only slightly from monocular (235, 426, 481). Sherrington (426), discounting the slight differences [that have now been shown to be real by Ireland (235) and by Thomas (481)], concluded that binocular fusion was a 'psychic' act superimposed on the physiologically separate monocular mechanisms. Further physiologic study of central interaction between the representations of the two eyes may offer alternatives to Sherrington's conclusion.

### *Auditory Space Perception*

Analysis of central interaction between paired sense organs has been pushed further for the ears than for the eyes [see Chapter XIV in this *Handbook*, Vol. 1, p. 610]. In cats, dogs and monkeys, the two ears are represented at each medial geniculate body (and at the auditory cortex) by partly overlapping populations of neurons. Stimulating both ears simultaneously, or in rapid succession, produces definite signs of interaction; the corresponding electrical responses are not a simple summation of those to separate stimulation of the two ears (405). The elegant analysis by Rosenzweig (405) of evoked responses in cat cortex suggests cortical (and subcortical) correlates for various stereophonic effects.

BINAURAL PARALLAX. In man, binaural localization of sounds has long been known to utilize differences in the relative intensity (396) and arrival time (2) of stimuli at the two ears. If two sounds (e.g. clicks) delivered by earphones are balanced for loudness and arrive simultaneously at the two ears, the listener hears a single ('fused') sound in or near the mid-line (inside or just above his head). As arrival times or intensity relations are altered, the (subjectively) single sound shifts toward the leading ear, i.e. the side of earlier arrival or greater intensity (380, 507). If one varies intensity and time relations in directions opposite to each other, very large intensity differences (over 10 db) are needed to counterbalance differences in time of less than 100 μsec. For loudness-balanced clicks, time differences of less than 30 μsec. can be effective in producing the impression of an off-center sound. Thresholds for duality (two clicks heard, one in each ear) are rarely reached with intervals below

1.5 msec. It has often been suggested that the neural basis for response to the minute time differences involved in lateralizing clicks must be some spatial separation in the central nervous system of the impulses corresponding to the two asynchronous stimuli (172, 240, 380).

It is obvious that these stereophonic phenomena are analogous in several ways to the experiments on binocular stereopsis. Both sets of experiments suggest mechanisms capable of a degree of accuracy which is difficult to reconcile with the supposed imprecision of central nervous connections. Moreover, for visual and auditory space perception, actual achievements exceed what is possible under the restricted conditions of a motionless observer. A stationary listener can judge sounds as emanating in the median plane, or to the left or right of it, but his sensory information is ambiguous in other respects, e.g. as to whether the sound is in front or in back of him. In more natural settings, where head movements are not restricted, such confusions do not arise. As Wallach (517) has shown, normal auditory localization utilizes the sequential changes in binaural stimulation which occur systematically as the observer moves his head through space. The ubiquity of this form of auditory motion parallax can be illustrated by the way in which it fails when the observer is given misinformation regarding the relationship between stimulus motion and body movement.

AUDITORY LOCALIZATION DURING HEAD AND BODY MOVEMENTS. Assume that the observer can rotate his head in a holder to the left or right while listening to a sound directly in front of him. If the sound source (in a dark room) is made to move with every head movement (so that it keeps its relative position to the head), the listener perceives it directly above his head (and not in front of him); it is from this overhead position that the ears would normally continue to receive invariant stimulation, in spite of varying rotation of the head to the left or right (517). If the listener is permitted to tilt his head (and not only to rotate it), the mislocalization disappears. An identical mislocalizaton can be obtained by keeping the observer motionless inside a rotating striped drum. The sound source, which is stationary, is again directly in front of the observer (but invisible to him because it is outside the drum). The striped drum is rotated at sufficient speeds to induce illusory motion of the observer's body in the direction opposite to that of the vertical black stripes. At this point, the sound is again perceived as directly overhead (517).

These simple experiments underscore the crucial role of normal patterning in the relation between movements of the observer and the corresponding relative motion of stimuli for the proper maintenance of spatial organization.

### *Interaction Between Posture and Distance Receptors in Spatial Localization*

It is also obvious that localization of external events usually involves concurrent perception of one's own posture. This information enters into the 'constancies' of perceived direction in space.

EFFECTS OF BODY TILT: THE AUBERT PHENOMENON AND ITS VARIANTS. When we tilt our heads, vertical lines in the environment remain vertical as if the signals generated by the postural change were able to counteract precisely the inclination of lines on our retina. The precision is diminished when a tilted observer attempts to set a luminous line to the vertical in an otherwise dark room [Aubert's experiment in 1860 (13)]. With moderate lateral body tilts (up to 30°), the settings are close to the true vertical but deviate from it in the normal adult by several degrees in a direction opposite to the tilt of his body, i.e. there is overcompensation or overconstancy [the 'E-phenomenon' of Müller (354)]. With larger body tilts, the correction for abnormal posture undershoots instead, and the line is set so that it falls short of the true vertical in the direction of the body tilt [the original Aubert phenomenon (13), or 'A-phenomenon' of Müller (354)]. Quantitative information on the effects of body tilts beyond 30° is scarce and insufficient to permit an analysis of the underlying mechanisms (in terms of feedback-control theory), as has been accomplished so convincingly by Mittelstaedt (349) for visuopostural interaction in the praying mantis and by von Holst (503) for fish orienting themselves in abnormal gravitational fields.

For moderate tilts (30° and less) there is considerably more information. The effects here are not limited to vision, but exist analogously in the tactile and auditory spheres. A tilted subject, blindfolded, adjusts a palpated rod to the vertical in such a way that he overcorrects by a few degrees, although congenitally blind subjects do less so (47). Again, blindfolded subjects, tilted to 30° to their right or left, adjust a single (ambient) sound to the apparent

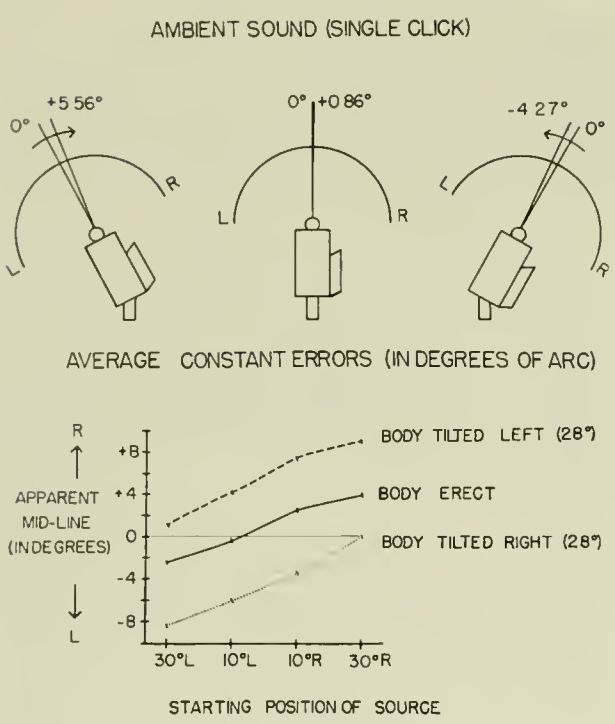



FIG. 24. Auditory localization under conditions of body tilt. *Above:* Normal adults set a sound source off to the right when they are tilted 30° to their left, and off to the left when they are tilted to their right. Thus, while tilted, the subjective 'straight overhead' position of the source deviates from its objective overhead position. *Below:* Plot of mid-line settings (in degrees of arc) as a function of body position and of starting position of the source. Note that starting a trial by moving the source from the subject's left or right results in characteristic starting position errors as long as the subject's body is tilted. [From Teuber & Liebert, unpublished observations.]

overhead position with consistent errors, so that their settings deviate to the right when they are tilted to the left, and conversely (476; see fig. 24).

The effects vary with age. The compensatory displacement increases progressively in the visual task from ages 6 to 19 as demonstrated by Wapner & Werner (522). For the auditory task, it has been shown by Liebert & Rudel (323) that the displacement grows progressively from 0° (at ages 5 to 6) to 6° at age 17. These results may be related to the fact that adaptation to body tilt is more marked in small children and diminishes with age. Thus, after a body tilt of 30° (lasting for 30 sec.), normal 5-year-old children, blindfolded, consider themselves upright when they are in fact still tilted an average of 14° to the side of their former tilt. This error diminishes to 4° (in the same direction) by age 17.[20]

The experiments just described all involve localization of stimuli under conditions that combine abnormal posture with minimal or absent visual fields. The resulting errors of localization are absent or minimal in a normal visual scene. It must be remembered further that even though posture, in these experiments, deviates from normal (i.e. upright), the postural system can be assumed to signal its deviation from the gravitational vertical in essentially normal fashion. The situation is different when there is misinformation about one's actual posture, as in a centrifuge (or circling aircraft) when the force acting on the body becomes a resultant of gravitational and centrifugal forces. Position of the body and of visual targets [e.g. a collimated star in the dark, see Graybiel (169)] are misperceived.

OCULOGRAVIC EFFECTS AND RELATED PHENOMENA. Mach (332) thought that these illusions corresponded exactly to the resultant of forces acting on the labyrinth, but this is not true (543), except (approximately) in a dark room (169). These 'oculogravic effects' are very much diminished in the presence of a patterned visual scene. Similarly, the illusory displacements and drifts of single lights or sounds [the oculogyral effects of Graybiel & Hupp (170) and the audiogyral effects of Clark & Graybiel (89)], after acceleration or deceleration, are maximal in an otherwise dark field and reduced under normal visual stimulation.

### *Abnormalities of Space Perception after Cerebral Lesions*

The complex interaction among sensory (and motor) systems in normal space perception makes it likely that abnormalities after cerebral lesions can take many forms, differing with the site of the lesion and the tasks employed to demonstrate the deficits. Analysis of these effects is incomplete, even for man, and scarcely begun for infrahuman species (466).

[20] The marked adaptation to body tilt in young children may not only be a function of vestibular adaptation as such. In the same series of experiments, Teuber & Liebert (476) and Liebert & Rudel (323) showed that young children are more readily influenced by the starting position of stimuli (535) on a variety of psychophysical tasks. Thus, in adjusting a click to the overhead position, children will set the sound source somewhat to the right, if the trial is begun with the source to their right, and to the left, with the source starting to their left. These 'starting-position effects' diminish progressively with age according to Liebert & Rudel (323) and Rudel, Teuber & Liebert (manuscript in preparation).

It is already clear, however, that there are different aspects of spatial organization in man that are rather selectively affected by different brain lesions. Such a picture then does not agree with the simple and traditional view of a unitary change in spatial orientation, for example the so-called 'visuo-spatial agnosia' [cf. Nielsen (362)], which should follow lesions in a restricted area such as the posterior parietal lobe. There are at least three fairly distinct forms of spatial disturbance that can be ascribed, provisionally, to occipital, frontal and parietal involvement.

DISTORTIONS IN THE TRIDIMENSIONAL STRUCTURE OF VISUAL SPACE. After acute lesions of occipital (or occipitoparietal or occipitotemporal) regions, visual space may be deformed in a systematic fashion so that objects seen in an affected (homonymous) half-field or quadrant are consistently mislocalized (31, 32, 469). Most frequently, objects are seen too far ('teleopsia') and conjointly as too small ('micropsia') compared with their appearance in less affected regions of the field. The disturbance can be demonstrated with variations of the three-needle experiment (31); in the stereoscope, there are difficulties with binocular fusion and distortions akin to those produced in normal subjects wearing aniseikonic lenses (6).[21] The disorder is found in the absence of any demonstrable impairment of cerebellar function, postural sensations or (peripheral) vestibular reactivity. The syndrome may persist for months after acute occipital lobe lesions, but is rarely found several years after injury (469). However, at these later stages the distortions may appear transiently during paroxysmal changes in visual function ('visual fits'), in which the EEG shows focal alterations. Curiously, these paroxysmal visuospatial disorders are significantly more frequent with lesions of the posterior lobe substance in the right (rather than left) hemisphere.

In rare instances, extreme disarticulation of visual space may occur during a fit (469), or a migraine attack (41) in which there is optic allesthesia; objects seen instead of appearing in their appropriate places in the visual field seem to lie elsewhere, e.g. in the opposite half-field, sometimes with 180° inversion in a diagonally opposite quadrant. Similar forms of allesthesia can be encountered in the somatosensory sphere with lesions at various levels [see Critchley (95) for review].

ABNORMALITY OF VISUOPOSTURAL INTERACTION. A more subtle, but equally intriguing alteration can be found after lesions of the anterior lobe substance. Men with penetrating gunshot wounds of the frontal lobes (right, left or both) tend to show an exaggerated compensatory error in setting a luminous line to the vertical when their head and body are tilted (Aubert task) [see Bender & Jung (27) and Teuber & Mishkin (478)]. The effect is an enhancement of the 'normal error' (E-phenomenon) described above; it may also exist for auditory settings, but data are incomplete on this point. Nor do we know the minimal effective lesion. In studies of acute brain injury or disease, Bender & Jung (27) showed that the exaggerated errors occurred with frontal and frontoparietal lesions. Abnormal errors appeared not only when the patients were tilted, but when they were upright; the luminous line was then set with a constant inclination away from the affected lobe. These errors in the upright position, first described by Goldstein (161), apparently disappear gradually, since they are not found in the late stages after anterior brain lesions (478) where body tilts are needed to uncover the abnormal interaction between visual localization and posture. Figure 25 summarizes a series of experiments employing Aubert's task and several variations and revealing the rather surprising specificity of the symptom.[22]

'SPATIAL DISORIENTATION' AFTER PARIETAL LESIONS. The most obvious forms of difficulty with spatial relations are those seen in parietal lobe involvement

[21] None of the studies here reviewed describe the peculiar syndrome of 'loss of depth' reported by Sir Gordon Holmes (218) as an occasional consequence of occipitoparietal lesion. Complete 'flattening' of the visual scene is difficult to conceive; perhaps the patients in question experienced diminished rather than absent depth. The issue cannot be decided as long as there are no experimental studies of space perception in such instances.

[22] Further analyses of changes in the Aubert phenomenon after cerebral lesions (477) have shown that settings of the vertical (with body tilted) can reveal two kinds of change: the specific one (viz. the exaggerated overcorrection after frontal lesions) and a nonspecific one. If one extracts the so-called starting-position effects (see footnote 20), one finds that groups of patients with brain injury in any lobe, and regardless of presence or absence of particular sensory or motor symptoms, manifest significantly larger starting-position effects than do matched controls. These enhanced starting-position effects are also found in children with brain damage tested on the auditory analogue of the task (Rudel, Teuber & Liebert, manuscript in preparation). By contrast, these children do not show the specific effect (found in adults with frontal lesion) until they reach early adolescence.

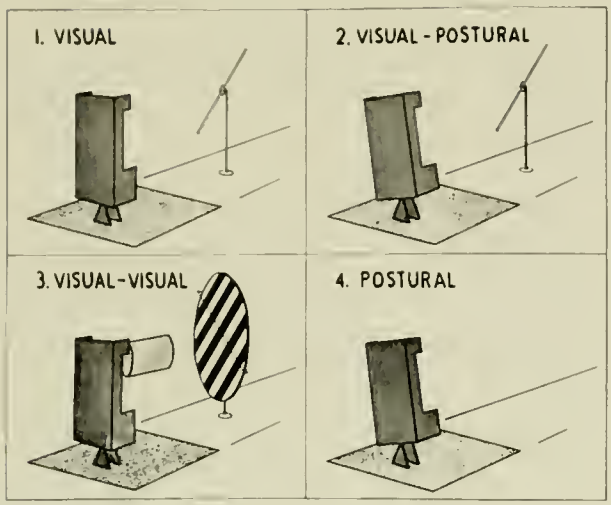



FIG. 25. Diagrams of four experiments on spatial localization. Two of these experiments (the *visual-postural* and *visual-visual* tasks) have been shown to yield differential results after frontal and posterior brain lesions in man. On the first and fourth tasks (*visual, postural*), normal adults and adults with frontal or parietal lesions perform in similar fashion; all three groups can set a luminous line to the vertical with very little error as long as they are upright (*Experiment 1*), and all three make similar errors in bringing themselves back to a vertical position after varying periods in a chair tilted 30° to right or left (*Experiment 4*). However, if required to set a luminous line to the apparent vertical with body tilted (*Experiment 2*), the frontal group makes greater errors than the other two (in the direction opposite their body tilt). In the *third experiment*, a black thread has to be set to the apparent vertical against an interfering background with oblique stripes and the body is kept upright. In this situation, the men with posterior brain lesions make much larger errors (in the direction of the stripes) than the controls or the men with frontal lesions. [From Teuber & Mishkin (478).]

(95, 114). Disorders in finding one's way about, even in familiar surroundings, and difficulties with dressing and with the verbal distinction of various body parts, all have been described as representing more or less specific types of agnosia or apraxia. Experimental analysis of these troubles (especially in their more subtle manifestations) suggests that these clinical designations may be misleading. Thus, disorders of route-finding are probaly not a 'visuospatial agnosia,' since the disorder is as great or greater when vision is excluded from the task (see fig. 26, 27).

The task employed series of maps, presented through the sense of sight or touch (418). The subjects had to follow by locomotion routes laid out on these maps (see fig. 26). Errors in route-finding, under these conditions, were maximal in a group of men

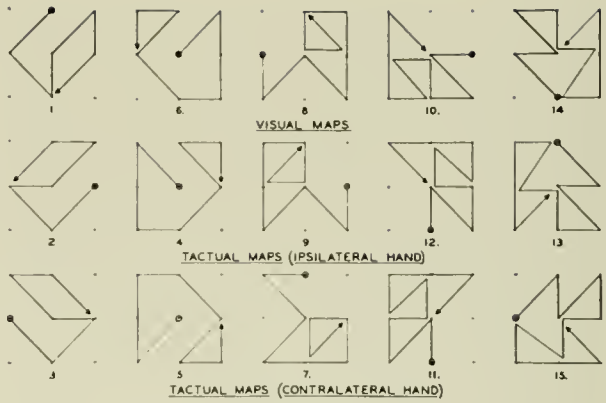



FIG. 26. Diagrams of maps used in route-finding test. The *nine dots* in each map represent nine circular red dots painted on the floor of a large room. In the room, adjacent dots are 137 cm apart, center to center. The subject is given each map in turn, in the order shown in the figure, and required to walk through the indicated path. The tactual maps are presented to the hand on the side of the brain injury (ipsilateral) or opposite the injury (contralateral); these tactual maps consist of string and tacks and are carried by the subject in a small curtained box which permits palpation but excludes vision. [From Semmes *et al.* (418).]

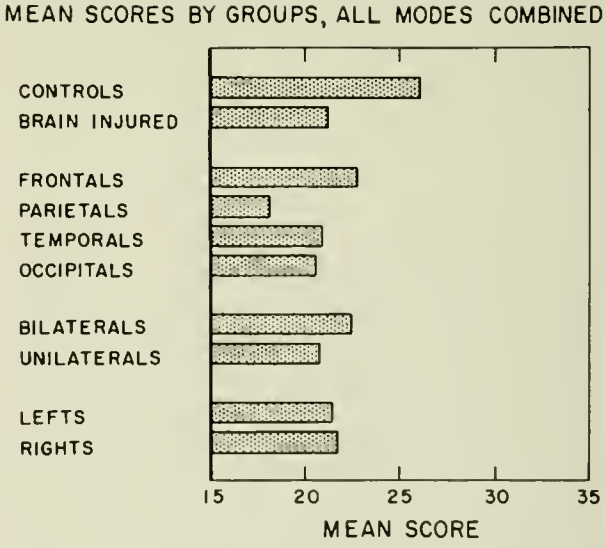



FIG. 27. Results of route-finding tests, grouped according to location of cerebral lesions. The score indicates the number of correct turns. The scores for the group with parietal lesions (and for that group only) are significantly below the scores earned by all other subjects, and by all other groups with injuries to the brain in the regions indicated (frontal, temporal, occipital); *left* and *right* refer to men with lesions involving the left and right cerebral hemisphere, respectively. [From Semmes *et al.* (418).]

with parietal lesions (right, left or bilateral), and appeared equally on the visual and tactile-kinesthetic versions of the task. In fact, when the results of the parietal group were eliminated from those of the total population with brain injuries tested, no differences between those with brain injuries and control subjects remained. The deficit thus was specific for parietal lesions, but independent of the sense modality through which the information was received. In this respect then, the disturbance was not an agnosia, since the term implies, in its traditional sense, a disorder limited to 'higher functions' within a single sensory modality.

Curiously, the group with maximal deficit on the route-finding task (in both its visual and tactile forms) also showed maximal impairment of tactile two-point discrimination (526), as if the underlying functions shared, at least in part, a common neural substrate. (The same patients, apparently, also show abnormally elevated thresholds for the detection of duality of dichotic clicks.) These unexpected patterns of symptoms suggest that seemingly 'simple' sensory deficits may be correlated with alterations in performance that in traditional terms would have been considered as 'complex.' For an experimental critique of agnosia, these results mean that we should be cautious before we assume that the organism should fall apart according to subdivisions of our textbooks. Defects in the nervous system may fail to divide the presumably lower and higher aspects of perception as neatly as can be done by a priori classifications.

### *Deprivation Studies*

DEPTH PERCEPTION AFTER EARLY VISUAL DEPRIVATION. Although the evidence is fragmentary, perception in subhuman forms may be increasingly less dependent on any particular perceptual experience as one descends the phylogenetic scale. We have mentioned the early appearance of depth perception after hatching in chicks (211); there is additional evidence that their pecking responses involve binocular vision from the start, in spite of the limited overlap of their monocular fields (212). Rats reared in darkness apparently show little perceptual deficit, since they can jump with nearly normal accuracy from platform to platform, adjusting the force of their jump to the visually perceived distance (310). In the most recent experiments of this type [by Walk *et al.* (515)], possible artifacts in earlier studies were minimized by placing dark-reared rats, on first exposure to light, near a 'visual cliff.' These tests, which eliminate the pretraining needed in the study by Lashley & Russell (310), are based on the assumption that, given a choice, an animal will not descend over a vertical edge toward a surface that appears to be far away. A 'near' and a 'far' surface was provided by placing two identical checkered fields, one to each side of a narrow horizontal runway. Horizontal glass plates of equal height extended to either side of the runway, but on one side the checkered field was immediately below the glass, and on the other side 53 in. below it. Nearly all of the experimental rats (reared for 90 days in the dark) descended on the 'near' side on first trial, just as did their normally reared litter mates. Such strong evidence for 'nativism' in depth perception is in apparent contrast to the disabling effects of rearing in darkness or unpatterned light for carnivores and primates (see above, p. 1622). The resolution may lie in genuine species differences (188) or in the greater side effects of restricted rearing in higher forms.

TACTILE DEPRIVATION: EFFECTS ON BODY SCHEME. Only one study has extended the 'early deprivation' paradigm to the tactile-kinesthetic sphere. Nissen *et al.* (363) encased all four limbs of a 4-wk.-old chimpanzee in cardboard cylinders which extended from elbows and knees to beyond the fingers and toes. Interrupted only for occasional testing and for refitting of the cylinder as the animal grew, the deprivation extended for 30 months. After removal of the cylinders, the chimpanzee was able to perform visual size, form and depth discriminations within normal limits, but had abnormal difficulties in learning such a simple tactile-kinesthetic task as turning its head to the side on which its fingers had been stimulated by firm pressure.

The results of this study (unless explained by some atrophy of disuse) recall the common belief that tactile and postural orientation is acquired in the form of 'schemata' as the result of use of the various body parts [see Head (186) and Oldfield & Zangwill (366, 367)]. Sudden removal of a part (as by amputation) uncovers the schema in the form of a persistent phantom limb. In keeping with these interpretations would be the absence of phantom limbs after removal of limbs that had been anesthetized or denervated for long periods prior to their loss (177, 178, 186, 475). Additional evidence on these phenomena is needed, particularly with respect to the consistent finding that tactile functions (touch-pressure, point localization, two-point discrimination) are better on an amputation stump than in the homologous portions of the intact limb (177, 178, 475).

This sensory reorganization seems maximal in those amputees who report that their phantom limb has become telescoped with time, so that it now seems to lie in or near the tip of their stump (177, 178).

### *Recombination (Rearrangement and Disarrangement) Studies*

PERSISTENT SPATIAL DISORIENTATION IN LOWER SPECIES. Space perception in lower vertebrates, and in birds and rodents, seems to arise autonomously, irrespective of early experience and use, in correspondence to their motor coordination which has been shown to be independent of practice (436, 437, 439, 530, 531). The same autonomy of central patterns that makes these species immune to early sensory deprivation leaves them helpless in the face of abnormal changes in sensory input, as after inversion of their visual fields (438) or transplantation of cutaneous nerves (437). After surgical rotation of their eyes or cross-connection of optic nerves, newts attack a lure in diagonally opposite parts of their visual field where the lure is not, and these mislocations persist indefinitely without correction. Newly hatched Leghorn chicks do no better when they are fitted, on emerging from the egg, with rubber hoods bearing binocular prisms that displace all visual objects laterally by several degrees; their pecking responses are correspondingly displaced. These responses become less scattered (as in normal chicks during the first few days after hatching), but this development only diminishes the variations in the distance by which they miss their target (212). The distance itself remains the same, reflecting exactly the visual displacement imposed by the prismatic spectacles.[23]

[23] One form of central compensation has nevertheless been described for fish and frogs. After unilateral destruction of a labyrinth, the ensuing corkscrew motions in fish (503) and the characteristic forced attitude (tilt toward the injured ear) in frogs (287) gradually disappear. This adaptation which resembles the gradual disappearance of Bechterev nystagmus in man (after unilateral section of the eighth nerve) has a definite time course (6 to 8 wk. in *Rana temporaria* and 6 to 8 mo. in *Rana esculenta*), but the underlying mechanism remains obscure. Leaving aside the possibility of regeneration in the eighth-nerve system of fish and amphibian, one must consider the potential role of supersensitivity in the denervated vestibular nuclei which eventually restores the balance between deafferented and intact halves of the central vestibular complex (Sharpless, personal communication). It should be noted, however, that the disappearance of the body tilt (in *Rana esculenta*) is reputedly hastened by low spinal transection, and delayed by forebrain removal or section of both optic nerves [and this even in animals kept in the dark (287)].

ADAPTATION IN MAN TO PROLONGED VISUOSPATIAL INVERSION OR DISTORTION. Corresponding experiments on man suggest that prolonged wearing of inverting or displacing spectacles leads to more readaptation than in lower forms. Yet, the course and limit of this adaptation still need to be defined. The classic experiments by Stratton (on himself) have been quoted equally as showing complete visuospatial reorganization (53) and complete failure of reorganization in anything but the motor sphere (521). Stratton inverted his visual field by wearing a telescope over one eye (occluding the other) for 21 and 87 hr., respectively. He reports in diary fashion that there was partial adaptation to the inverted scene (455–457). Yet, when he saw the world as upright, he felt as if his head were inverted!

Ewert's three subjects (including himself) wore binocular inverting telescopes for 175, 193 and 195 hr., respectively, during 2 weeks (116–118). His reports focus on motor readjustment (as assessed, e.g. by card-sorting tests) and give less detail on the appearance of the visual scene; there seems to have been less perceptual adaptation than in Stratton's study. Complete adaptation, however, has been claimed for the one subject (Snyder) in Snyder & Pronko's experiment in which a binocular device was worn for 30 days (431).

As Walls (521) has pointed out, the binocular spectacles used in these experiments actually represented a pseudoscope, since they reversed not only up and down but interchanged all binocular disparities. The same was true of the device worn by the one monkey tested by Foley (128); his animal carried inverting binocular telescopes for one week. When one wears such a device, distant objects seem to approach as one walks backwards, and the monkey developed a propensity for moving backward throughout the testing period. She also acquired a habit of looking at the world through her legs.

By far the most thorough studies of this type, however, are those undertaken over many years in Innsbruck by Erismann and Kohler [reported by Kohler (285, 286)]. In their work, the devices employed provided either right-left reversals of vision, or up-down reversals, but not both simultaneously, as in all the earlier studies. They paid equal attention to motor readjustment and to possible perceptual changes and tried to measure the course of both, their ultimate extent, and the aftereffects when the spectacles were removed after periods of continuous wearing (extending, in some of their subjects, to as

much as 4 mo.). The resulting observations are a severe test for any theory of perception.

It is clear from Kohler's reports that motor readjustment precedes 'perceptual' readjustment by days or weeks. Both motor and perceptual reorganization seem 'easier' with up-down than with right-left reversals. There are large individual differences in rate and extent of readjustment, and there may be systematic differences with age. Motor readjustment (especially to up-down reversals) goes quite far, permitting subjects, after 2 weeks or more, to engage in fencing, skiing or riding a bicycle in heavy traffic. There still remain tendencies, however, to make 'false starts,' and these persist to the end of the experimental period. In the perceptual sphere, adaptation is peculiar (Kohler says 'unreasonable'), in that there seem to be piecemeal readjustments within the scene. With right-left reversing spectacles, subjects may report at some stages that they 'see' cars on the correct (right) side of the street and hear the engine noises as emanating from the correct side, yet the cars bear license plates in mirror writing. With up-down reversing spectacles, subjects note, with amazement, that snow falls steadily downward past trees that are seen as upside down. There are similar but reversed 'piecemeal' effects when the glasses are removed.

The aftereffects are particularly variable from subject to subject. For instance, apparent tilts of the scene, with every tilt of one's head, can last for 2 weeks following removal of right-left reversing spectacles (that had been worn continuously for 24 days). Another subject, after wearing the same spectacles for 37 days, reached a stage of 'nearly correct perception,' but complained of diplopia (including monocular diplopia) for some time after the glasses had been removed.

PARTIAL SPATIAL REORGANIZATION DURING SHORT-TERM EXPERIMENTS. It will be apparent that in spite of these detailed and sensitive reports, much remains to be done to delineate conditions for adaptation and to explore the curious aftereffects. In view of the difficulties of the long-term experiments, there has been renewed interest in analogous short-term studies involving rearrangement or disarrangement of perceptual inputs. Some improvement of eye-hand coordination during the first hour of wearing prisms (laterally displacing the view of targets and hand) was noticed already by von Helmholtz (501). Wundt (552) reported the gradual disappearance of distortions and displacements of contours (metamorphopsiae) after an inflammatory process in his own retina had been arrested; he compared this apparent adaptation to the overcoming of 'dioptrically induced metamorphopsiae,' i.e. the distortions imposed by prisms or imperfect lenses. The prism effects were restudied by Gibson (151) who observed that the colored fringes gradually disappeared (to reappear, briefly, in reverse orientation when the prisms were removed); the apparent curvature of (objectively) straight lines also diminished, and on removal of the prisms, objectively straight lines seemed curved slightly in the opposite direction. Most important was Gibson's insight that the prism acted merely as a means for producing curved lines. The same effect could be obtained by looking at a curved line with bare eyes for several minutes; during this period, the line became (subjectively) less curved, and this effect could be measured by the amount to which, immediately afterwards, an objectively straight line had to be curved in order to appear straight. Analogous effects can be found on prolonged inspection of straight lines deviating by some degrees from the objective horizontal or vertical: their deviation diminishes on prolonged inspection (152, 153, 158, 281, 388). Effects of this sort, obtained in a particular region of the visual field, are essentially restricted to that region; if obtained on monocular inspection, the effect 'transfers' to the other eye (281).[24]

A possible binocular analogue is the gradual adaptation to aniseikonic spectacles which distort one monocular view against the other in a particular meridian (6, 77). Reduction in the various subjective distortions of depth, distance and size (see above) occurs at different rates in different observers and remains fractional in relatively unstructured environments [e.g. in Ames' 'leaf room' which lacks the usual vertical and horizontal lines (6)]. In normal

[24] These changes in spatial organization on prolonged inspection of particular stimulus patterns are much smaller in extent than the gradual 'righting' of a complex scene, e.g. a room seen through a slanting mirror (9, 536) or of an actually tilted room viewed from an adjustable tilting chair (10). When viewing such a room which is actually tilted by 30°, many subjects accept the room as upright, especially if their own body, on the chair, is tilted 30° with or against the tilt of the room. There are, however, large and fairly consistent individual differences in the extent to which subjects are influenced by the visual scene under these and similar conditions. Witkin, whose interests have turned lately to these individual differences, ascribes greater 'field dependence' in such tasks to female as compared with male subjects, and to children as compared with adults (544).

environments, the adaptation is said to progress more rapidly and to go further (77). [Curiously, the distortions are rarely immediate on donning such aniseikonic lenses; there is a noticeable latency of seconds or minutes before the onset of the metamorphopsiae (539).]

'REAFFERENT' STIMULATION AS PREREQUISITE FOR ADAPTATION. Most of the studies reviewed thus far indicate some partial reorganization of space perception in man. Hardly any of the studies, however, lend themselves to an experimental analysis of stimulus conditions that might be necessary or sufficient for such adaptation. The experiments by Held on short-term exposure to 'recombined' (atypical) stimulus patterns attempt to do just that. Influenced by the earlier experiments of Wallach (517) on auditory localization by a moving observer (described above), and by the theories of von Holst & Mittelstaedt, (505), he proposed that one of the crucial prerequisites for adaptation (e.g. to prisms) is some orderly relation between sensation and the sensory consequences of self-produced motion.

In a typical experiment, prisms of equal power are placed over the eyes, with bases either left or right. This causes a lateral displacement of the visual scene, accompanied by corresponding errors in eye-hand coordination and in egocentric localization (visual direction finding). The errors in eye-hand coordination can be measured in a device (193) which permits the subject to see his own hand as well as the target pattern which he has to mark manually while wearing the prisms; the device, however, prevents him from seeing the marks he makes, so that he lacks any information about his success or failure. In spite of this, the errors diminish steadily through marking sessions lasting less than an hour. The errors are likewise diminished if the subject merely views his hand while moving it actively to and fro. Conversely, viewing his hand while it is being moved passively by another person is ineffective in producing adaptation to the altered sensory input (194). Similarly, subjects who walk about actively in a patterned environment while wearing the prisms show significant reduction of mislocalization (errors of egocentric localization) at the end of a 1-hr. period. If, instead, the subjects are pushed about the same path in a wheelchair, no significant adaptation takes place (Held & Bossom, unpublished observations). Finally, if the static prisms are replaced by rotating prisms whose power is changed continuously, adaptation is made impossible (Cohen & Held, unpublished observations).

The interpretation of these experiments is facilitated by introducing a distinction made by von Holst (504) between afferent stimulation (produced by the environment) and reafferent stimulation (produced by the active motion of the perceiver). Stability and orderliness of perceived space would then depend on the existence of certain invariant relations between afferent and reafferent activities. Normally, head tilts are accompanied by converse tilts of the visual vertical. If one assumes a corollary discharge from motor to sensory systems accompanying the active tilt, then the sensory (e.g. visual) apparatus is prepared to counteract the ensuing optical tilt. Such a negative feed-back mechanism, once established, turns into a maladaptive positive feedback on wearing spectacles which reverse right and left. Yet the facts of (at least partial) readaptation suggest that the nervous system is capable of extracting new invariants as the atypical stimulation continues. Removing the spectacles will then, of course, lead again to maladaptive reactions—the previous adaptation turns into an illusion, although the relatively briefer course of these aftereffects indicates either the preponderant weight of the much longer 'normal' exposures, prior to the experiment, or, perhaps, an innate bias of the system in favor of certain invariants. Experimental evidence is much too fragmentary thus far to permit one to assign relative weights to the role of exposure history on the one hand and of prior structural determinants on the other.

DOUBLE LOCALIZATION: MONOCULAR DIPLOPIA AND DIPLOPHONIC EFFECTS. There may be important limits in the plasticity of perception as here described. The supposed adaptation of spatial perception to unilateral squint is a case in point. Not only is there a curious reduction in pattern vision of the squinting eye (see above, pp. 1622–1623), but there frequently is monocular diplopia in that eye; this curious disturbance of spatial organization becomes particularly manifest after the good eye is lost (as occasionally happens) and only the squinting eye remains. Consistent double vision with such a single eye has been described in several instances; the best studied case is that of Bielschowsky (44) where the diplopia was found to persist until the patient died, 16 years after the loss of his better eye. As noted above, a similar monocular diplopia has been described by Kohler as a sequel of protracted prism experiments (286),

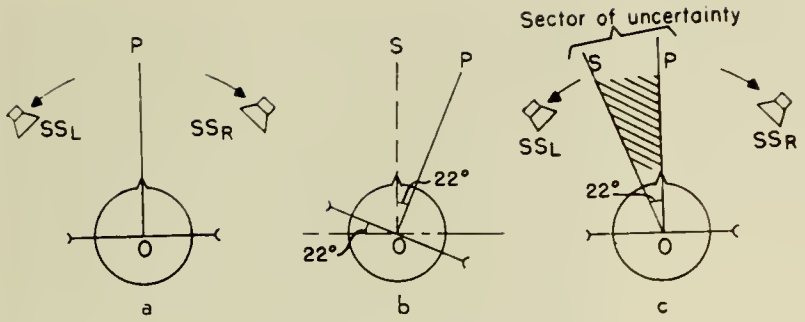



FIG. 28. The diplophonic effect. *a:* Before exposure; observer (*O*) wears pseudophones with axis normal; *P*, primary direction of 'straight ahead' sound source; $SS_L$, sound source on left; $SS_R$, sound source on right. *b:* Exposure condition: observer wears pseudophones with axis rotated by 22° so that the left ear 'leads.' Sounds emanating from *S*, the original (and anatomical) 'straight ahead' position, seem at first displaced by about 22° to the observer's left; his auditory 'straight ahead' is at *P*. Walking forward or backward induces illusory motions of the sound source. *c:* After exposure: observer has worn pseudophones as described under *b* for 7 hr. in his usual environment. The axis of the pseudophone has now been reset to normal, and the observer's sound localizations are tested in an anechoic room where he tries to locate concealed sound sources ($SS_L$, $SS_R$) by turning his head and body towards their supposed location. Although only one source is emitting sounds at any one trial, the observer reports that he hears two sound sources simultaneously, or that the source could be localized in two different directions. A source located at *P* is perceived simultaneously at *P* and at some point *S*, to the left of *P*. Sounds emanating from directions intermediate between *S* and *P* all seem to be straight ahead. [From Held (192).]

and there are analogous observations in the short-term prism experiments reported by Held and his co-workers.

A direct analogy in binaural localization is the diplophonic effect—the subjective doubling of an objectively single sound source—in Held's studies involving pseudophones (192). Figure 28 illustrates one of these experiments in which the subjects wore a pseudophone arrangement continuously for several hours during their regular working day. The device, in effect, rotated their interaural axis by 22°, thus giving one ear an abnormal 'lead' over the other. In subsequent experiments, it could be shown that the gradual reduction in mislocalization of sounds could be accelerated or retarded (and even reversed) by controlling the conditions of exposure while the pseudophones were in place. Thus, making the subjects walk along a prescribed path in an anechoic room, while listening to concealed loudspeakers, diminished the mislocalization if the subjects were made to walk straight toward or away from the hidden sound source. Under these conditions, the difference in arrival time of the sound at their ears remained invariant during self-induced motion. Various other paths led to less correction or even to deterioration of localizing performance.

If one looks back upon these numerous studies on normal and abnormal space perception, we begin to see some possible phylogenetic differences which we failed to demonstrate convincingly in our review on perception of shape. The modifiability of spatial organization in higher forms (even though in need of further empirical delineation) is in sharp contrast to the rigidity of spatial organization in lower forms. In time it should be possible to find those aspects of perception that are specific to man and thus correlated with the fact that he alone among animals has developed language.

It is also clear that all of the data on space perception and its changes after cerebral defects, or its readjustments to radically altered inputs, suggest that spatial projection in the nervous system—the retinotopical projection and its counterparts in the somatosensory and auditory spheres—may represent necessary but hardly sufficient neural conditions for the tridimensional organization of perception. As the organism changes its position relative to the environment, space has to be continuously reorganized as the result of interaction between postural systems and contact and distance receptor fields. How to conceive of this physiologic achievement, we can hardly guess. Anticipatory and facilitory discharges from motor into sensory systems have been postulated as one indispensable correlate by Lashley (304, 307),

von Holst & Mittelstaedt (505) and Sperry (438); but the existence of such corollary discharges remains conjecture. It is certain, however, that neither pattern nor depth perception can be studied without an appreciation of perception of motion in the environment, of self-produced movement and of the reafferent stimulation that results from the movement of the perceiver himself.

## PERCEPTION OF APPARENT MOTION

In classical psychophysics, with its assumption of one-to-one relation of stimulus and response, there was no problem of perception of motion. Things were seen to move because their 'image' moved over the retina, or felt as moving over the skin because the stimulus did. Attention had to be directed to various forms of motion perception in the absence of a moving object before the psychophysiologic problem of motion could be discovered. There are four main classes of apparent motion, viz. afterimages of motion, induced motions, autokinetic effects and, most importantly, stroboscopic motion. Each of these four sets of phenomena has been considered an illusion of motion, but the perceptions engendered are indiscriminable for the observer from 'real' motion. The physiologic basis of each of these apparent motions, and of true motion, are likely to be the same.

### *Afterimages of Motion*

Various aftereffects of seen and felt motion were known to Purkinje (392) (who also described illusory motions following vestibular stimulation). The most familiar laboratory demonstrations are the waterfall illusion and the rotating spiral. In the former, a horizontally striped surface is moved vertically upward or downward in the observer's frontal plane. The pattern induces apparent motion, in reverse direction, in its (stationary) surroundings; when the pattern itself is stopped, there appears an afterimage of movement that is negative, i.e. opposite in direction to the previous (objective) movement of the pattern (545). In demonstrating the spiral aftereffect, one rotates a disk with a spiral pattern in front of the observer. During rotation at moderate speeds, the spiral pattern seems to expand or contract, and these complex motions are transposed, temporarily, onto stationary patterns to which the observer shifts his gaze. The device, usually called Plateau's spiral after its inventor (383) also induces various subjective colors during rotation. Stationary patterns with high redundancy, as those studied by MacKay (336), likewise produce apparent motion during and after inspection (see fig. 29). These motions are complementary, i.e. their direction is at right angles to the static contours in the stimulus array.

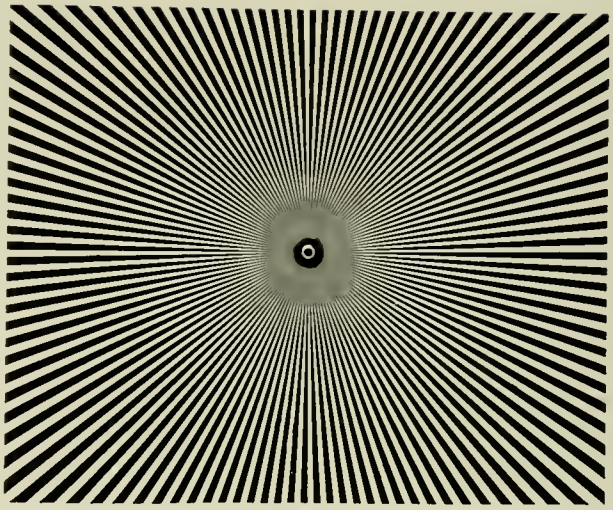


FIG. 29. Stationary visual pattern with high redundancy which induces moving images. The *radiating lines* produce shimmering effects on prolonged inspection and aftereffects of wavy lines moving in circles at right angles to the stimulus lines. This complementary aftereffect (following 10 sec. inspection of the pattern) can be projected on a gray surface where it is seen to rotate clockwise (predominantly) or counterclockwise. There is no simple correlation with handedness. [From MacKay (336).]

### *Induced Motion*

Induced motion is familiar to anyone who has seen the moon 'race' through interrupted clouds. Here the true motion of the surround (the clouds) is assigned to the (stationary) moon. Analogous phenomena can be obtained in the laboratory [e.g. Duncker (110)] where a luminous rectangle and a luminous dot within it can be made to move, separately or together, in an otherwise dark room. Moving the rectangle ordinarily leads to perception of motion for the enclosed dot; moving the rectangle and the dot over a given distance, but in opposite directions, leads to perceived motion of the dot within a (subjectively) stationary rectangle over the combined distance, etc.

More complex motions can be generated by a device constructed by Johansson (241, 242) which permits analysis of resultant motion perception when

two spots of light in a dark room are engaged in independent periodic motions, e.g. along straight paths at right angles to each other. The resultant perception does not image the 'true motions,' but depends crucially on their phase relations. Johansson suggests (241) that the observer performs an analysis into component vectors. Such analyses can be noticed in natural settings, e.g. when we see a friend waving to us from a moving train. The actual motion of the hand is sinusoidal but is perceived as a combination of linear progression (of the train) and up-and-down motion (of the waving hand).

It is tempting to speculate on the neural mechanisms that might be required in extracting such component vectors from complex motions. Is it the same mechanism that generates complementary apparent motions on inspection of regular stationary or moving patterns (336), or negative afterimages of movement? The problem of attributed or induced motions has considerable generality. Motion is usually perceived as carried by objects, and object character implies either an ability to move relative to a stationary surround or (in the case of stationary objects) to be seen in relative motion as the perspective of the observer changes. So considered, problems of motion perception are continuous with those of object recognition and of spatial organization [see above, and Gibson (154, 156)].[25]

*Autokinetic Effects*

Perhaps the most striking instance of motion perception in the absence of objective movement (of stimuli and observer) is the phenomenon of autokinesis; a single spot of light in a dark room, after a few seconds of inspection, appears to engage in erratic excursions (84, 284). The direction and extent of these motions are influenced by many factors, including posture, expectation or even suggestion (425); but knowledge of the illusory character of the movements does not abolish them. The movements stop, however, as soon as the surrounding room is made (even faintly) visible. Apparently, a single spot without visual framework is not an adequate stimulus for spatial localization (284); the observer cannot even point at such a dot with his finger (411). Eye movements can affect extent and direction of autokinetic motions but cannot explain them (175). The phenomenon casts serious doubts on theories of spatial localization invoking simple retinal 'local signs.'

*Stroboscopic Motion*

The principle of moving picture projection is a succession of stimuli directed at discrete retinal loci. This principle was known early in the nineteenth century to physicists like Faraday (120) and Plateau (382) who constructed stroboscopic devices generating apparent motion by serial presentation of static patterns. These effects were considered a 'peculiar class of optical deceptions,' errors of judgment rather than basic sensations. Only Exner (119) argued forcefully for their basic sensory character; he pointed out that the compound eyes of invertebrates might be organs of motion perception *par excellence*—an argument not lost on his distinguished nephew, Karl von Frisch. It was clear to Exner that an adequate hypothesis about the neural mechanism underlying motion perception should encompass all forms of 'illusory,' as well as 'real' motion. This hope was heightened by Wertheimer's justly famous study (536) of apparent movement which gave rise to Gestalt psychology.

Wertheimer simplified the stimulus conditions. Instead of continuously repeated displacements (as in the usual stroboscope), he presented a single pair of targets (luminous dots or simple lines), *a* and *b*, separated by a variable time interval, *t*, and by a variable angular distance, *s*. With long intervals (over 200 msec.), his observers reported succession. They saw first *a*, then *b*, each in its place. With short intervals (less than 30 msec.), they perceived *a* and *b* simultaneously, flickering in their respective positions. With intervals intermediate between 30 and 200 msec., the observers reported movement, with optimal movement at about 60 msec., where neither *a* nor *b* were seen, but a single object moving smoothly over the track defined by *a* and *b*. At intervals longer than those for optimal motion, various partial motions were obtained; it was in this range that Wertheimer's subjects noticed 'pure motion,' an impression of disembodied movement from *a* to *b* without the impression of a moving object. He called this particular phenomenon 'pure phi'—the first of a number of Greek letter designations for

[25] Beyond this, study of relative motions of two dots in homogeneous fields has suggested to Michotte (347) that there might be psychophysical correlates for perception of causality. If one dot slowly approaches another stationary dot, then stops, and, if then the formerly stationary dot begins to move, the compelling impression for most observers is that of an impact which launches the second dot on its path. These demonstrations are similar to those dealing with 'physiognomic' qualities of movements carried by abstract geometric figures (189).

various phenomenal types of movement [see Boring (53), pp. 596–597, for an inclusive list].

The report was followed during the next two decades by more than 100 other studies of apparent motion. Many of these were concerned with further quantification of the interval $t$ and the distance $s$. [The earlier studies are summarized in Koffka's chapter (283) on motion perception in Bethe's *Handbuch*; for later reviews, see Neff (359) and Graham (166).] Results were at times discordant as to details, and it became clear, soon after Wertheimer's report, that his values for $t$ (e.g. 60 msec. for optimal movement) did not necessarily hold in other experimental settings. Nevertheless most of the later studies have confirmed the basic sequence (from perceived succession via optimal motion to simultaneity) and the crucial role of the interval $t$ in determining these stages. The complex interdependence of $t$, $s$ and the intensity of stimuli ($i$) is usually specified in the form of Korte's 'laws' (289) of apparent motion which can be stated briefly in the following set of formulas [see Boring (53) and Graham (166)]:

$$\text{If } i = \text{const.}, t_{opt} \sim s; s_{opt} \sim t.$$
$$\text{If } t = \text{const.}, s_{opt} \sim i; i_{opt} \sim s.$$
$$\text{If } s = \text{const.}, i_{opt} \sim 1/t; t_{opt} \sim 1/i.$$

Thus, for a given intensity $i$, the time interval $t$ between the stimuli has to be increased (decreased) as the distance $s$ is increased (decreased), in order to maintain optimal motion. For a given time interval $t$, the same direct relations hold between $i$ and $s$; as one is changed, the other has to be changed in the same direction to keep the perception of motion invariant. Finally, if the distance $s$ is held constant, $i$ and $t$ vary reciprocally; for instance, an increase in intensity has to be counterbalanced by decreasing the interval, and conversely.

There are difficulties with these expressions which make it unwise to call them 'laws'; the upper and lower limits of their validity need to be defined. There are some contradictory experimental results even in the midrange of values (360), and there is an unfortunate ambiguity in the parameter $i$ which is meant to designate luminous energy as well as area of the targets (166). However, it is possible, in principle, to give these expressions the precision obtained in parametric studies of other sensory dimensions and to obtain an isokinetic surface which defines conditions of optimal motion perception (in direct analogy to isochromatic and isophonic contours, depicted in figs. 1 and 2). Such an isokinetic surface would lie in a tridimensional space, in which $s$, $t$ and $i$ are coordinates specifying conditions of optimal movement. Outside of the surface, and to one side of it, would be the conditions for simultaneity; to the other side, those for succession.

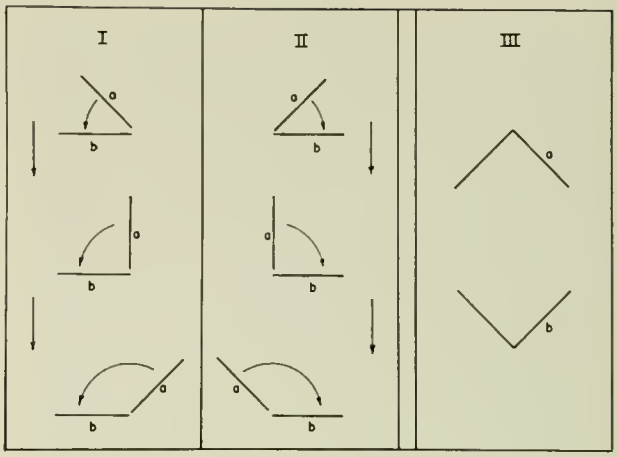



FIG. 30. Effects of recent exposure history and of stimulus configuration on the path of apparent movement. *I*, *II*: After repeated exposure of lines *a* and *b*, at intervals leading to apparent motion from *a* to *b*, observers continue to report motion from *a* to *b* over the paths indicated by *curved arrows*. *III*: The two V-shaped patterns *a* and *b*, if alternately exposed in the positions shown, lead to apparent motion through the third dimension, in and out of the projection surface, thus maintaining the shape of the V. [Adapted from Wertheimer (536), Koffka (283) and von Schiller (508).]

Undoubtedly, other factors in addition to $s$, $t$ and $i$ can enter into the determination of apparent motion effects, such as earlier exposures (see fig. 30), or special colors or shapes of the targets (fig. 30). Ambiguous patterns can be designed which permit alternative motions to be perceived (508). Some of these patterns have been used in tests of cerebral dominance by Jasper (239) and Carter (86). However, the most important aspect of apparent motion is the observer's inability to discriminate optimal apparent motion from real motion of a single target over the same path (100, 106, 360), and the remarkable interchangeability of spatial and temporal determinants expressed in the formulas given above. Another and simpler way of demonstrating this interchangeability is to project three spots of light, A, B and C, in a dark room so that they form a horizontal line with the middle dot, B, equidistant from A to the left and C to the right. If A and B are made to alternate slowly (but within the range of apparent motion), and B and C more rapidly (though still within that range), then the distance from A to B

will appear longer than the distance from B to C. Analogous effects can be obtained by producing tactile apparent motion on the skin (198, 498).

TACTILE AND AUDITORY APPARENT MOTION. Any physiologic theory of stroboscopic effects must take account of their occurrence in other sense modalities beside the visual one, and of their presence in lower animals. Nonvisual apparent motion effects in man are best established for tactile stimuli applied serially in separate places on the body surface (35, 36, 81, 498). Under appropriate conditions, observers report the stages of phenomenal succession, optimal motion and simultaneity, depending on time intervals, spatial separation, pressure employed and other factors. Some experimenters had no difficulty in confirming Korte's 'laws' for touch [e.g. Burtt (81)], but others found more exceptions to these rules in touch than in vision (36, 225, 414). Training and attitudes seemed to play a considerable role in some of the tactile effects, particularly in apparent motion from one hand to the other (35, 36). Most experimenters, however, observed a maximal shortening in the perceived distance of the two contacts with optimal movement (414); in one of the earliest studies, von Frey (498) obtained shortening of up to 25 per cent.

Apparent motion likewise exists in audition, although the experimental facts for that modality are somewhat less clear. Burtt (80) simply used two sound sources in a dark room; by varying their distance and intensities, and the interval between them, he elaborated a set of relations between $s$, $i$ and $t$ analogous to Korte's laws for vision. Others, including Scholz (414), were less successful in this respect. Further experiments are needed, particularly since the stimuli for apparent auditory movement can be made much more compelling by using a stereophonic arrangement employing dichotic clicks. By continuous shifting of their time or intensity relations below the duality threshold, one can obtain particularly convincing forms of apparent auditory movement (506). Note that the minute time differences that are effective here are not perceived as such, but are heard as changes in localization or as a movement in the case of a continuous change.

STROBOSCOPIC EFFECTS IN SUBHUMAN SPECIES. For the visual modality at least, stroboscopic effects have been demonstrated convincingly in animals below man. Monkeys react to moving pictures (e.g. of other animals) as if to a real scene (259). In birds, a puzzling structure within the eye (the pecten) has been claimed to serve as a shadow caster which converts any continuous movement across the retina into successions of stimuli (343). By producing a lattice of shadows, the pecten could in fact enhance retinal on-and-off effects for patterns transported across the photoreceptors (96). If this is true, then 'real motion' for birds would be just as discontinuous as stroboscopic motion within the range of their pecten.

For fish, there are two experiments showing responses to apparent motion under conditions where the same perceptual effects occur in man (206). Thus, Gaffron (138) utilized the tendency of minnows (*Phoxinus laevis*) and sticklebacks (*Gasterosteus aculeatus*) to follow a moving striped pattern. The test pattern was rotated with variable speed behind a sectored disk spun at constant speed (20 rps). When the striped pattern reached a speed where the direction of movement of the stripes seemed to reverse itself for human observers, the fish turned around and swam in the direction of the 'illusory' motion. Still more telling are the experiments by von Schiller (509). He trained minnows (*Phoxinus*) to discriminate between screens with a vertically moving dot and those with a stationary dot; then he introduced two dots, alternating at varying rates, and established that the minnows could be trained to discriminate what were, for man, simultaneous and successive phases of apparent motion, on the one hand, from real motion, on the other. However, the fish could not maintain the discrimination when time relations of the apparent motion stimuli were adjusted to produce what was, for man, the optimal stage of apparent movement. For minnow as for man, optimal apparent motion seems equivalent to real motion.[26]

[26] It is puzzling that convincing reports of apparent motion perception are lacking for invertebrates. Gaffron (138) failed to obtain such effects in dragonfly larvae and houseflies under experimental conditions she had used successfully with fish. Further work with cephalopods and with invertebrates with compound eyes is needed. Some of the studies on motion perception in lower vertebrates also require repetition and extension, for instance the much quoted experiments by Beniuc (34), Lissmann (325) and Brecher (60) on *Betta splendens* (the Siamese fighting fish). As they stand, these studies do not bear on motion perception as such, but on perception of flicker and fusion. The range of parameters explored does not permit the conclusion that fusion thresholds for intermittent visual stimulation are higher in *Betta* than in man, nor do the results suggest that *Betta* "sees all motions at half the speed seen by man" (206).

*A Physiologic Hypothesis*

The phenomenal identity of apparent (optimal) and real motion suggested to Wertheimer (536) and to others after him, including Köhler (268) and Helson & King (198), that whatever the stimulus for any form of motion perception might be, it need not be a continuous movement across the receptor surface. Instead Wertheimer postulated a central correlate — a continuous 'phi'-process within, presumably, the visual cortex; there, points *a* and *b* are represented in correspondingly separate loci, *a'* and *b'*, according to the principle of retinotopical projection. At appropriate time intervals the excitation in *a'* is 'drawn over' to the excitation in *b'*; corresponding to this 'physiological short circuit,' we perceive movement from *a* to *b*. Analogous assumptions can be made for tactile motion perception (utilizing the principle of somatotopic projection) and for auditory movement (by assuming that certain time differences in the auditory system are translated into spatial separation). The postulate of a psychoneural correspondence in motion perception formed the core of Köhler's isomorphism (267, 272) which assumes a general correspondence in the spatial and temporal order of perceptions and their underlying neural (cerebral) events. As Bartley has discussed in Chapter XXX of this *Handbook*, Köhler has attempted to test this hypothesis by recording d.c. potentials from the occipital scalp while the subject sees a pattern move across his visual field (277–280). The theory of isomorphism has no particular difficulty in accounting for apparent (and real) movement across the normal blind spot (446). In this case, the retinal substrate is discontinuous, but the cortical substrate is not (20). The theory, however, is embarrassed by the fact that apparent motion can be obtained across acquired scotomata, i.e. blind spots produced by cerebral lesions (474). We shall return to these observations later; they bear particularly on the phenomenon of 'real' motion.

## PERCEPTION OF 'REAL' MOTION

If it is true that 'apparent' motion represents a limiting case of 'true' motion, then the distinction between the two is unfortunate. The distinction has led to a relative neglect of true motion, so that quantitative information on perception of true motion is sparse; where available, data are limited by failure to survey a sufficient range of stimulus conditions.

*Characteristics in Normal Subjects*

MINIMAL RATES. A few experiments bear on the question of thresholds for motion perception. There is a minimal rate of displacement for a moving stimulus below which observers may note a change, but not real motion. Aubert (14, 15), under rather restricted conditions, found a minimal rate of 1 to 2 min. of arc per sec.; later, Brown (66–68) obtained values between 2 and 3 min. of arc per sec. under somewhat less favorable conditions. Such thresholds obviously vary with size and pattern of moving stimulus, with pattern of surround, with illumination and with numerous other factors.

Surprisingly, there are not even adequate data for minimal rates in peripheral as against central parts of the retina, and this in spite of the general belief that motion detection in peripheral regions of the visual field is disproportionately better than other forms of acuity. Likewise there is no reliable information on thresholds for visually perceived acceleration. If motion thresholds are defined as the minimal angular distance traversed (with rate held constant), values can be cited that suggest a minimal detectable extent of 20 sec. of arc (22). This is less than the minimum angle for the resolution of two acuity objects, a result anticipated by Exner in 1875 (119). Others, however, such as Gordon (163), have reported that values for displacement and for resolution thresholds are similar, at least under dim illumination. The issue remains unresolved, in the absence of studies for a wider range of rates, illuminations and retinal positions. For the same reasons, we cannot be certain whether lower vertebrates might have better capacity for motion detection than man, as Honigmann (223) has claimed for toads.

DIFFERENTIAL THRESHOLDS. The thresholds for discrimination of two different rates of motion had not been determined directly until the recent studies of Ekman & Dahlbäck (111), although apprehension of differential speeds are involved in so-called motion parallax investigated by von Helmholtz (501, 502) and others (56, 167, 512). Thus, von Tschermak-Seysenegg (512), improving upon an earlier set-up by Bourdon (56), determined the minimal detectable distance between two pins along the line of regard when the observer looked at them with fixed gaze or with moving head and eyes. Under the second condition, there is differential angular movement of the pins (relative to the observer's eye) as long as the pins are at different distances from the eye. The aver-

age error of setting the pins while moving the head and eyes is much smaller than with fixed gaze; motion parallax seems to aid in detecting depth. For this reason, von Tschermak-Seysenegg (512) called his device a 'parallactoscope,' by analogy with the stereoscope. In a further development of these techniques, Graham *et al.* (167) designed an apparatus permitting the observer to judge separation in depth of two pins moving at identical rates (but at variable distance along the line of regard) before the observer's stationary eye. The situation involves, in essence, apprehension of differential velocities under rigorously controlled conditions. Graham *et al.* (167) obtained the remarkably low threshold (for velocity difference) of 30 sec. of arc per second of time. Finally, an ingenious variation of parallactoscopy is represented by the shadow-caster arrangements employed by Gibson *et al.* (150), in which the shadows of two random dot patterns are superimposed on the same screen (thus controlling accommodation) and moved at independently varying rates. The effect for most observers is one of separation of the two arrays in depth, indicating the close connection between motion and depth perception which Gibson (154) has stressed.

The device also lends itself to further studies of the ways in which differences in velocity are seen—a matter investigated under simpler stimulus conditions by Ekman & Dahlbäck (111) who elaborated a subjective scale of velocity. Using the psychophysical method of fractionation, they obtained a function relating subjective to objective velocity according to a power law, as Stevens (451) would have predicted. The exponent $n$ in this particular instance turned out to be 1.77, indicating that perceived velocity increases nearly as the square of the objective velocity of a moving target.

By far the most thorough studies of perceived 'real' motion are those of Brown (66–68). In his experiments, the moving objects were small black squares pasted 20 cm. apart on endless white bands, spun at variable speeds behind a variable opening (the widest opening being 2 x 15 cm.). A stationary fixation point was provided in the center of the opening. This simple device permitted the study of real motion as a function of objective rates of movement, size of moving objects, size of opening traversed, distance of the device from the observer, illumination and presence or absence of perceptible structure in the surround. By placing two devices side by side, and varying one or several factors in one of them, the observer could be asked to set the other in such a way as to keep certain perceptual effects invariant.

Outstanding among Brown's results are the following: different thresholds for different perceived stages of movement; the crucial role of the surround; the equally crucial role of size of moving object and opening; the so-called transposition of perceived velocities with changing size; and the relative 'constancy' of perceived velocity with varying distance from the observer's eyes.

PHENOMENAL STAGES. Table 1 gives the thresholds obtained by Brown for the four major stages in perception of real motion. We have already mentioned the first threshold for minimal rate (2 to 3 min. of arc per sec. of time); below this speed, motion can be inferred from changes in position of the object (as for the hour hand of a watch) but cannot be perceived. At speeds above this threshold range, motion is seen. It is at this stage that the seen movement is indistinguishable from optimal apparent motion produced stroboscopically over the same distance. As speed of the moving belt is increased, a second stage is reached—that of apparent reversal in the direction of movement; the moving square appears paradoxically at the far end of the opening and seems to jump back toward the point where it enters. With still higher speed, a third stage comes in where the observer reports seeing two or several squares for every single square that traverses the opening. With (slight) further increases in speed, the observer reports fusion; instead of seeing one or several black squares, he sees a gray streak covering their track.

Table 1 indicates to what extent threshold values tend to overlap; nevertheless, the sequence as such can be demonstrated with striking regularity. Paraphrasing Brown (68), we can say that a future physiologic theory of perceived movement must explain both 'real and apparent movement, phenomenal velocity, increase in the number of moving objects, the thresholds for fusion, and the impression of duration produced by watching objects in motion.' This means that a really satisfactory theory of any

TABLE 1. *Thresholds of Four Stages in Perceived Real Motion**

| | |
|---|---|
| 1) Minimal rate | 2–6 min. of arc per sec. |
| 2) Apparent reversal | 3–9 deg. of arc per sec. |
| 3) Apparent multiplication | 7–15 deg. of arc per sec. |
| 4) Fusion | 12–32 deg. of arc per sec. |

* Data from Brown (68).

one of these phenomena ought to account for all the others.

ROLE OF SIZE AND SURROUND. The importance of the surround in motion perception is strikingly demonstrated by requiring observers to equate perceived velocities for two moving bands which are identical except for the fact that the opening, or frame, is homogeneous in one case and covered with dots or lines in the other. Motion through the second, or 'structured' field appears faster, just as a rider who enters the woods after traversing an open field seems to double his speed. Similarly, movement seems faster when either the frame or the moving object is reduced in size, the latter effect being the same as one's tendency to overestimate the speed of small animals, for instance a scurrying mouse.

VELOCITY TRANSPOSITION. Much less expected is Brown's discovery of transposition of perceived velocities. The experiment, again, consists of asking the observer to equate the speeds of two endless belts at equal distances from his eyes; however, for one belt, all dimensions are reduced, e.g. the width of the opening and the size of the moving squares are half those of the other. In that case, the observer will approximately double the rate of motion of the smaller display in order to obtain an impression of velocity equal to that of the larger.

As Wallach has pointed out (516), this result seems closely related to the outcome of experiments which demonstrate relative 'constancy' of perceived velocity; two displays of identical size are placed at different distances from the observer, e.g. one twice as far as the other. Under these conditions, observers increase the objective speed of the more distant display only very slightly in order to obtain impressions of velocity equal to the less distant display. If rates of stimulus motion across the retina were all that mattered, then the display twice as far away should be set at double speed for the impression of equality. The fact that nearly equal velocities, at different distances, are perceived as equal has of course considerable biological utility, even though this constancy of perceived speed is far from perfect, indeed, significantly less than the relative constancy of perceived size [because of this discrepancy, Wallach (516) is reluctant to 'reduce' speed constancy to size constancy].

Clearly, the phenomena of speed constancy are equivalent to those of transposition; the distant display is proportionately smaller (on the retina, at least) and the higher subjective velocity thus, in effect, counteracts this diminution in size. An unresolved question remains: is transposition the primary phenomenon [as Wallach (516) prefers to assume] or is transposition a case of constancy misapplied? One could argue that with displays equidistant but differing in size, the observer performs a 'correction' in perceived speed that would have been appropriate if the difference in the scale of the two displays had been due to differences in distance. If his reasoning holds, then velocity transposition would be a particular instance of a whole class of illusions which are actually constancies of perception running off *in vacuo*.

'PARADOXES' OF SEEN MOTION. Several other puzzling aspects of motion perception, although less well known, are important for any attempt at constructing a physiologic theory of perceived movement. Apparent velocity of moving objects varies not only with retinal area stimulated (faster in foveal regions), but also within the fovea, depending on whether the observer moves his eyes or not. Following an object in motion with moving eyes leads to impressions of somewhat lower speeds, as compared with the same objective motion observed while fixating at a stationary point. The effect is called the Aubert-Fleischl paradox (14, 15, 126); it may be related to whatever mechanisms provide us ordinarily with a stationary environment when our eyes sweep over it. The Aubert-Fleischl rule was called a paradox because its originators felt that pursuit movements of the eyes should increase the impression of motion of a moving object. However, if the relative motions of objects during eye movement have to be somehow counteracted, then the paradox may be lessened; it may again reflect a tendency towards constancy (in this case of perceived movement during motion of receptor structures) which overshoots to reduce an impression of real motion.

Acuity (for resolution of moving targets) is markedly diminished during attempted pursuit movements of the eyes, and this the more so, the more rapid the motion of the target, as shown by Ludvigh (329). He attributes this effect to the decreasing alignment between target and eye with increasing speed (and hence, increasing blurring of the image). Maximal blurring occurs during the rapid saccadic movements of the eyes [e.g. from fixation to fixation in reading, cf. Woodworth & Schlosberg (549, pp. 500–510)]. This blurring is so marked that some of the early investigators of eye movements, such as Dodge (108)

and Woodworth (548), felt it made it unnecessary to postulate a 'central anesthesia' of vision during such movements (219). More recent disclosures of 'suppression' of incoming sensory information by means of centrifugal control of sense organs [see Granit (168)] suggest that the issue might deserve to be reopened.

There are other curious effects. A target moving through a frame at certain speeds appears to 'jump' into view, i.e. it is not seen at first as it enters the opening, but 'further along,' at some distance from the anterior edge of the frame. The phenomenon has been studied by Fröhlich (134) in the hopes of obtaining a measure of minimum time needed for any perceptual act, but the stimulus situation is probably too complex to provide a basis for estimating an observer's *Empfindungszeit* (sensation-time), as Fröhlich (134) had hoped. Actually, there is not only the delay (or rather displacement) in the appearance of a target that traverses a diaphragm; an analogous effect is noted when the target disappears—it is last seen at some distance from the edge of the opening, rather than right at it. More promising for intensive study is the Hazelhoff effect (185). This effect is obtained on looking at a moving target (e.g. a square traveling across a screen); on sudden and momentary exposure of a dot (projected by a tachistoscope onto the square), the observer perceives the dot at some distance ahead of (and outside of) the traveling square.[27]

### *Abnormalities of Perception of Motion*

The phenomena of 'real' and 'apparent' motion which we have reviewed demand a physiologic interpretation, but such an interpretation is lacking. Some clues for physiology may be gained by surveying next those alterations of motion perception that result from defects in the neural substrate, from sensory isolation or from recombination (involving rearrangement or disarrangement of relations between receptors and central nervous system).

ALTERED MOTION PERCEPTION AFTER CEREBRAL LESIONS. We can begin with evidence from defect experiments. It is commonly thought that cerebral lesions implicating central visual pathways tend to produce greater impairment for pattern than for motion perception (399). The evidence for such a statement, however, is unconvincing. It is not unexpected to find areas in defective visual fields where targets are perceived when they are in motion but not when they are stationary. The movement takes the target over a wider angular extent in the field and thus produces more stimulation. Moreover, the movement prevents the abnormally rapid fading that is found in some (though not all) defective visual fields (25, 26). Actual measurements of thresholds for apparent (and real) motion in such impaired regions of the visual field [e.g. after penetrating lesions of man's geniculostriate system (473)] demonstrate that motion perception is impaired *pari passu* with defects in the forming of contours; a target has to move through wider angles or with greater acceleration for its motion to be perceived. Thresholds for apparent motion are correspondingly raised in the same regions of the visual field, i.e. the rate of alternation of two (stationary) targets has to be higher before stroboscopic effects are reported (473). Again, in the same regions there is a characteristic decrease in the critical rate at which a single intermittent light appears to be fused (i.e. the critical flicker frequency is reduced). These concomitant changes result in a loss of stroboscopic effects for particular stimulus conditions; the patient with lesions of the central visual pathways may perceive the succession of (slowly alternating) stimuli, but their alternation seems to him abnormally rapid. A slight increase in their rate of alternation leads immediately into the stage of simultaneous flicker, and a further increase leads to fusion of each target without any intervening stages of apparent motion.

These abnormalities of motion perception are remarkable because of the regular association of alterations in the perception of apparent motion, of flicker fusion and of real motion, suggesting that all of these phenomena share a common physiologic substrate. Furthermore, these threshold changes are accompanied by qualitative changes in the appearance of true motion. In impaired portions of defective visual fields, the perception of a continuous motion is frequently dissected into a series of multiple stationary images, quite analogous to the phenomena obtained for normal observers in Brown's experiments (68) when the target speed exceeded certain values. (Thus, one patient with a gunshot wound of the right occipitotemporal region complained that when a motorcycle passed him to his left, he saw instead "a string of motorcycles standing still.") There may be a uniform basis for both the normal and abnormal forms of polyopia (473). Analogous changes can be

[27] There may be a curious auditory analogue of this effect (Broadbent, personal communication to Dr. Richard Warren). If a click is interposed somewhere within a tape recording of a sentence, listeners err considerably in saying at what point within the sentence the click has occurred.

observed at certain stages of intoxication by mescaline (262).

The common factor underlying the changes in motion and flicker perception might be an abnormal interaction of stimuli successively applied to the injured neural substrate. This interpretation is suggested by results of two-flash experiments with patients who (on standard perimetric tests) appeared to have normal vision in their foveal region but homonymous defects in the periphery of their visual fields (24). If a conditioning flash is presented to the fovea, and followed within critical time by a test flash to the same area, the threshold for the first flash may be normal, but that for the second flash greatly raised. These observations suggest an abnormal recovery cycle; the injured visual system takes longer than the intact one to recover from the effects of the first flash. The abnormality is found even when the first flash is presented to one eye and the second to the other.

There may be analogous abnormalities in the temporal interaction of tactile stimuli following lesions of central somatosensory pathways (238, 444, 445). As Weinstein has shown (525), parietal lobe lesions in man produce exaggerated time errors for weights. In normal subjects, successive application of two weights, e.g. to the supported hands, leads rather regularly to an overestimation of the second weight (so-called negative time error). This normal perceptual error is markedly enhanced after parietal lobe lesions. Apparently, unilateral lesions of either parietal lobe suffice to produce this exaggerated time error which is found, curiously, in both hands (ipsilateral and contralateral to the parietal lesion).

It has been argued that these and similar disturbances of interaction (between simultaneous and successive stimuli) might be at the root of what is commonly interpreted as visual or tactile agnosia (25, 417, 466). Disorders of serial patterning of impulses, if sufficiently severe, could easily prevent recognition of objects through the affected sense modality. Such an interpretation of disorders in object recognition, after cerebral lesions, would thus be an alternative to the more traditional notion of a selective loss of higher ('apperceptive' or 'associative') function in the presence of seemingly intact sensory performance.

ISOLATION STUDIES. Disturbances in motion perception are outstanding among aftereffects of sensory deprivation. Patients 'born blind' (due to congenital cataracts) reputedly complain of continual illusory movements of objects in their environment after their cataracts have been removed by surgery (511). Unfortunately, evaluation of these reports is rendered difficult by the absence of adequate analyses of perception in the cases thus far reported, e.g. in the accounts compiled by von Senden (511). Clearly, visual performance after cataract extraction requires experimental study rather than casual description (538). The reports might mean, as Hebb (188) has suggested, that pattern vision after early and prolonged visual deprivation has to be learned, and that illusory motions result from an inability, on the part of the patient, to discriminate motions of his own eyes from those of the environment as long as pattern perception is imperfect. It must be noted, however, that the eyes of such patients are engaged in continual irregular and dissociated movements (an 'ataxia of gaze'); the data are insufficient to decide whether these oculomotor disturbances merely reflect the perceptual difficulties or are in some way their cause. The same peculiar ataxia of gaze, together with marked perceptual disturbances, has been noted by Riesen in chimpanzees reared in darkness or under uniform (patternless) visual stimulation (401).

In man, even temporary deprivation can lead to disordered motion perception during the first few minutes or hours following return to a normal visual environment. Thus, in the ingenious isolation studies sponsored by Hebb at McGill University in Montreal (40, 205), volunteer adult subjects were deprived of pattern vision for several hours or days. The subject was lying on a cot with translucent goggles covering his eyes; he wore earphones which delivered a masking noise and had cardboard gauntlets on his arms and hands. During the deprivation period, many subjects experienced hallucinations; upon release from confinement, they complained of illusory motion of objects seen; they also misjudged the apparent speed of real (visually apprehended) movements.

It is possible that analogous visual effects might be obtained after short-term exposure to a 'noisy' (maximally unstable) visual field, rather than a uniform stable field. Following exposures of as little as 30 min. to the 'snow' on a television picture screen, normal subjects markedly underestimate the actual speed of a moving test object (195). Conversely, prolonged exposure to a stable visual pattern leads to overestimates of visual speed. Areas of a normal visual field 'satiated' in such fashion show diminished flicker fusion, and apparent motion effects are also altered in the same way as in patients with defects resulting from cerebral lesions; the targets have to

alternate more rapidly for the occurrence of apparent motion (39, 101, 273, 423, 472).

RECOMBINATION (DISARRANGEMENT) STUDIES. Since motion perception is readily altered by injury to the neural substrate and by exposure to unpatterned or atypically patterned fields, it will be expected that disarrangement experiments should likewise produce abnormalities. Indeed, rotation of the eyes (producing an inverted visual field) leads to incessant forced movements in several lower species where such experiments have been performed. Thus, the fly *Eristalis* moves about normally inside a stationary drum with alternating vertical black and white stripes; as soon, however, as the head has been rotated 180° and fixed in this abnormal position (as is possible in this species), every movement of the animal produces paroxysms of circling (348, 505). The same forced circling is produced in fish with rotated eyes (438) when placed in an optically structured environment. This forced spinning is abolished by covering the eyes or by destruction of the optic lobes in the midbrain. By contrast, neither bilateral labyrinthectomy nor destruction (singly or together) of the forebrain, cerebellum or hypothalamus abolish this abnormal optokinetic reaction. In these fish, as well as in amphibians (436, 437, 439), such maladaptive response to surgical rotation of the eyeball seems to persist indefinitely without correction by re-education (439).

Inversion of the visual field in man (by means of inverting mirrors or prismatic spectacles) results in subjective motions of the visual scene, often with giddiness and nausea. In children (but rarely in adults) there may be forced movements and loss of postural control. However, in contrast to what has been observed in lower forms, i.e. in invertebrates (348), in fish (438) and in amphibians (436, 439), the inversion by spectacles in man is eventually tolerated with minimal motor disturbance (116–118, 431, 455–457). In the most elaborate experiments of this type by Erismann and Kohler [see especially Kohler's monograph (285)], there are reports of gradual readaptation of perception (taking several weeks), with elimination of illusory object motions and of righting of the scene. These perceptual adaptations are said to take consistently longer than the readjustment of motor performance (285). Following removal of the spectacles, all observers again experience illusory motions of the scene, especially on moving their eyes or head, and these disturbances last for several hours or days.

Interpretation of all these effects is needed before one can formulate a theory of perception. The problems of readaptation aside, abnormal (illusory) motion with inverted fields recalls the common observation that passive movement of the eyeball (by tapping against it) leads to an apparent movement of the visual scene. By contrast, normal ('voluntary') eye movements leave the visual field immobile.[28] In cases of paralysis of extraocular muscles, an intended eye movement (which fails to be executed because of the palsy) is accompanied by a subjective shift of the visual scene in the direction of the intended ocular movement. These curious illusory motions are also present after complete experimental immobilization of the eyeball by infiltration of the extrinsic eye muscles with procaine (288), a procedure which presumably paralyzes and anesthetizes the extraocular muscles, thus eliminating both movement and proprioception.

One attempt at interpreting all of these phenomena would be to invoke again a corollary discharge; any efferent discharge, leading to eye movement, is accompanied by concurrent central discharges into the visual system which anticipate and counteract those changes in visual stimulation that are most likely to result from the ocular movement. Such a self-regulating circuit would yield a stationary scene, as long as eye movement and shifting scene are in correspondence with one another (see fig. 31). If the eye is moved passively (without any concurrent central discharge), there is no compensation and the relative motion of objects on the retina is perceived as (illusory) movement of the surround. If the eye is paralyzed, efferent and concurrent discharge produce a compensatory shift of the visual scene which is again in error, since there is no ocular movement that needs to be compensated. Inversion of the eyes, or of the scene (as by spectacles), would turn the normal negative feed-back arrangement into a maladaptive positive feedback. The central compensatory discharge no longer counteracts but augments the apparent shift of the visual scene which accompanies every movement of eyes or head. This positive feed-

[28] In the normal subject, nystagmus of sudden onset (e.g. after barbiturate medication) leads to a corresponding subjective to-and-fro movement of the visual environment (oscillopsia). By contrast, patients with congenital nystagmus perceive a stable visual environment. These patients react to barbiturates, paradoxically, with a temporary cessation of their nystagmus. When the nystagmus returns (usually within 30 to 45 min. after medication), they complain, transiently, of oscillopsia and even of polyopia (29).

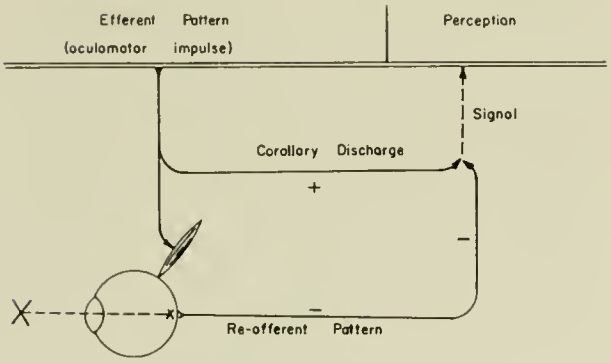



FIG. 31. Diagram to indicate postulated interaction between afferent, efferent and re-afferent processes in perception. Self-induced motion of the eye (efferent pattern) causes peripheral motor effects and, concurrently, a central discharge back into the appropriate sensory system (corollary discharge) which normally matches (i.e. cancels) the sensations produced by the active movement (re-afferent pattern). Under normal conditions, corollary discharges and re-afferent patterns balance, so that signals from the environment are perceived (e.g. motion of external objects) and distinguished from relative motions due to the perceiver's own movements. When the visual field is inverted, the same feedback becomes positive and maladaptive, causing subjective spinning of the visual field and (in lower species) forced movements of the body. See Sperry (438) and MacKay (335). [Adapted from von Holst (504) and von Holst & Mittelstaedt (505).]

back continues uncorrected in lower forms but can be readjusted apparently in man.

The hypothesis just developed is in essence a restatement of older views regarding a systematic (compensatory) shifting of retinal space values during eye movement (201, 214, 215). This hypothesis has been recast in feed-back terms, independently and simultaneously, by von Holst & Mittelstaedt (505) and by Sperry (438). Although entirely conjectural at this point, the hypothesis is attractive, since it can subsume normal and abnormal phenomena, and can perhaps be elaborated into a more general theory of constancies and illusions, and of perceptual identification.

## CONSTANCIES, ILLUSIONS AND FIGURAL AFTEREFFECTS

### *Constancies: Examples and Measurement*

Within limits, sizes and shapes of objects maintain approximate constancy as their distance and orientation changes. A man moving away from an observer is seen to recede but does not appear to shrink until a certain distance is exceeded; this is constancy of size. Neither does the apparent speed of his movements change as they take him further away; this is constancy of velocity (see above, p. 1644). A circle rotated out of the frontal plane is usually seen as a circle-at-a-slant and remains distinguishable from an ellipse produced by the corresponding geometric projection; this is constancy of shape.

These 'constancies' can be quantified by assuming that the actual perception departs more or less from the law of geometrical optics which predicts responses in accord with computed variations in the physical properties of the retinal image—hence 'law of the retinal image.' For the case of the circle-at-a-slant, the law of the retinal image predicts that the perceiver would match it with an ellipse with the same ratio of minor to major axis as that found in the geometrical projection of the slanted circle onto the observer's frontal plane. If the perceiver matches the slanted circle instead with an identical circle appearing in his frontal plane, we say that he exhibits complete 'constancy.' In actual experiments the choices usually fall between the prediction made by the 'law of constancy' and that made by the 'law of the retinal image.' (Very occasionally, there are instances of 'overconstancy,' however.) The incomplete constancy under these conditions has been variously called perceptual 'compromise' by Brunswik (73, 76), or 'partial regression to the real object' by Thouless (484, 485). Both investigators introduced simple expressions to describe such partial constancies in terms of ratios. The Brunswik ratio (73), *BR*, is the one used most frequently.

$$BR = \frac{R - S}{C - S}$$

where $R$ = a measure of the response (e.g. subject's choice of a matching shape or size, etc.); $S$ = predicted response according to the 'law of the retinal image'; $C$ = predicted response according to the 'law of constancy.'

This ratio ($\times$ 100) gives a per cent value of the extent to which the experimental results agree with the law of constancy. Thus, a Brunswik ratio of 1.00 indicates complete agreement—the observer matches circle with circle. A ratio of 0 indicates that there is no constancy, and that the circle-at-a-slant is matched with the particular ellipse that corresponds to its frontal projection.

The Thouless ratio (*TR*) is the same as the Bruns-

wik ratio, except that logarithms of $R$, $S$ and $C$ are employed:

$$TR = \frac{\log R - \log S}{\log C - \log S}$$

The meaning of the ratio values of 0 and 1.00 are the same here as for the Brunswik expression. Leibowitz (312) has indicated how these traditional ratios can be determined from power functions based on experimental results in which the independent variable (e.g. slant, distance, etc.) has been introduced for a wide range of values.

INTERPRETATIONS. Both von Helmholtz (501) and Hering (200, 202) knew that colors tend to look 'the same' under rather wide variations in illumination, but they differed profoundly in their interpretations of these phenomena. Von Helmholtz (501) believed that we learn to expect how any particular color should look under 'normal' white illumination. Changes in the light reflected by such objects, under different intensities of illumination, or under different colored lights, were then corrected by recourse to experience. The interpretation involved distinction of basic sensory from elaborative perceptual processes, with the latter acquiring a quasi-intellectual character; sensations became perceptions on the basis of 'unconscious inference.'

Hering (200, 202) agreed that phenomena of approximate color constancy represented "one of the most striking and important facts of physiological optics . . ." since without this ". . . a piece of chalk on an overcast day would appear as dark as a piece of coal on a sunny day and in the course of a day would take on all possible brightnesses between white and black." In accounting for the effect, however, he tried to avoid judgmental factors and attempted to reduce brightness constancy to such more tangible physiologic mechanisms as changing pupillary aperture, adaptation and contrast. In dealing with constancy under chromatic illumination, he nevertheless felt compelled to invoke individual experience: "All the things which are known to us from past experience . . . in respect to color are seen through the spectacle of memory colors" (200, 202).

CONSTANCY IN ANIMALS AND CHILDREN. Controversies about the interpretation of perceptual constancies have continued to this day. The role of higher judgmental processes has been made less likely when it turned out that animals below man showed similar or stronger constancy effects under comparable experimental conditions. Thus, Köhler (265, 266) showed brightness constancy in chimpanzees, while Locke (327) proved color constancy in rhesus monkeys; the effect in that species clearly surpassed corresponding effects in human observers. There are equally striking demonstrations of color constancy for birds [employing domestic chicks (252)] and cyprinid fish (78). There are similar, though less complete, results for tests of size and shape constancy in subhuman forms [Leibowitz (unpublished observations) and Zeigler & Leibowitz (556) for rhesus monkeys, Gunter (176) for cats and Götz (160) for chicks]. Studies of higher invertebrates are still to be made.

In apparent contrast to these univocal reports of strong constancy effects in subhuman forms are a series of studies purporting to show smaller constancy effects in young children than in older children or adults, e.g. the studies of Beyrl (42), Klimpfinger (258), Brunswik (73, 76), Piaget (375) and Lambercier (297). These accounts are contradicted by those of Frank (131), Burzlaff (82), Koffka (284) and Akishige (4).

THE NEED FOR PARAMETRIC STUDIES. There may be two main reasons for this lack of clarity: experiments in this area have rarely been sufficiently analytic, and too many investigators have assumed that different constancies should have a common base.

*a*) The first objection has been raised by Graham (166) and Leibowitz (313) who point out that few of the available studies have been 'parametric' in design; variables are not often sampled over a sufficiently wide range of values. For instance, by sampling size constancy functions over a wide range of distances, for groups of children and adults, Zeigler & Leibowitz (555) were able to show that the size-matching functions of the two groups were alike at close distances and differed as the distance of the objects increased. It was as if size constancy in young children did not 'reach out' as far into space as in older children and adults. Such a result reconciles several seemingly discrepant reports based on experiments restricted each to a single but different distance.

*b*) The second source of difficulties in this area is the common view that the many different constancy effects should reflect a single process. It is true that the varied constancies have identical biologic use; an animal should not misperceive a large predator as a small prey merely because the predator appears at a greater distance (504), and it should distinguish sounds that are soft but close from those that are loud but far (350). These accomplishments, however,

are probably based on diverse physiologic mechanisms. This has been shown, for instance, in parametric studies by Leibowitz *et al.* (314) on effects of tachistoscopic presentation upon constancy of shape, size and brightness. The same variable, viz. brief exposure, had differential effects on these three measures. Short exposure diminished shape constancy, had little effect on size constancy and enhanced brightness constancy. Similarly, tests of shape and size constancy have different outcomes when they are performed on photographs of the test objects rather than on the test objects themselves; in the photographs, shape constancy is reduced, while size constancy is virtually abolished. The experienced photographer takes these reductions into account when planning an exposure, just as he attempts (with varying success) to overcome his natural tendency towards brightness constancy which leads him, if unchecked, to overexpose his films at noon and to underexpose them at dusk.

RECENT WORK ON CONSTANCY OF COLOR AND BRIGHTNESS. The approach of Hering (but without recourse to memory colors) has been revived in the studies by Helson (196), just as the tradition of von Helmholtz continues in Brunswik's probabilistic approach (73, 74, 76) to constancy effects. Helson endeavors to show that adaptation and contrast suffice in explaining chromatic and achromatic constancies. In any patterned field, an 'adaptation level' is established which is the "weighted geometric mean of the reflectance of all parts in the visual scene." Under colored illumination, for instance in green light (as under the foliage of trees), the (greenish) background will contribute disproportionately to this adaptation level. All surfaces that have reflectances above adaptation reflectance take the hue of the (complementary) afterimage. Surfaces near the adaptation level are either seen as colorless or with very low saturation. In this formulation, chromatic 'constancy' is a consequence of adaptation (to the chromatic level) and of contrast which is, in turn, a consequence of gradients from the level. The adaptation processes postulated here, however, need to be faster than those ordinarily considered.

Helson's work is in close contact with the modern views on color vision represented by Hurvich & Jameson (231). In older views, 'black' is usually regarded as the one color which is due wholly to the eye. In fact, however, any color, in any saturation, can be evoked from positive or negative chromaticity gradients. In spectrally homogeneous yellow illumination, "samples of high reflectance are yellow, while those of low reflectance are reddish-blue"; or in monochromatic blue illumination, "samples of high reflectance are blue and those of low reflectance reddish-yellow. . . . The colors arising from either positive or negative gradients are equally 'good,' the latter appearing more saturated in strongly chromatic illumination than the former" (196).[29]

Attempts at reducing (achromatic) brightness constancy to simultaneous contrast or, more generally, to gradients of illumination in the visual field have likewise been made [see Wallach (518) and Leibowitz *et al.* (315)]. A complication in this area is introduced by the fact that brightness contrast appears to be primarily unidirectional; brighter objects depress the brightness of less bright objects, but the dimmer object seems to have little comparable effect on those of higher luminance. In experiments with a gray test object viewed over an illuminance range of 1 million to 1 against either 'black,' 'white' or 'gray' backgrounds (315), the major portion of the constancy effect could be predicted from independently derived contrast relationships.

Doubts have been expressed, however, whether all phenomena of brightness constancy can be thus explained (337). Several classic experiments reveal this difficulty. In Gelb's experiment (145) a black disk is shown in a dark room and illuminated by a spotlight. It appears white until a small piece of white paper is brought near it; at that moment the disk turns abruptly black. In the converse experiment by Kardos (248), a white disk is shadowed so that its surround remains brilliantly lit. Such a disk looks black until the shadow-caster is shifted so that a penumbra becomes visible; in that instant, the disk begins to look white, though shaded. This demonstration is essentially the same as the older ringed-shadow experiment introduced by Hering: a small object casts a shadow on a faintly illuminated white surface. The shaded area looks as white as the rest of the surface, though shaded. Draw a heavy black outline around the shadow and the shaded region turns dark gray. On obliteration of the penumbra, the shadow is changed into a stain (200, 202).

These three experiments (by Hering, Gelb and Kardos) are often invoked as instances detracting from an interpretation of brightness constancy in

[29] These facts form the basis of the much publicized demonstrations on color vision by Land (298) which illustrate the principles implicit in Hering's experiments on colored shadows (200, 202) and in the systematic quantitative work of Hurvich & Jameson (231).

FIG. 32. A distorted room (constructed by Ames) which induces apparent distortions of size. The window on the *left* is actually much more distant than the one on the *right*, i.e. the floor plan of the room is not rectangular. As noted in the text, it can be argued that the illusion merely shows failure of size constancy under conditions of 'reduction.' [From Lawrence (311).]

simple terms of contrast; the areas involved in these experiments differ too much. However, one can consider these demonstrations as proof for the crucial role of boundaries (or contours, as discussed above on p. 1605), and as evidence of the trigger action of the introduction of boundaries between areas of high and low luminance (in analogy to the demonstration in fig. 4, above). Undoubtedly, many additional factors need to be considered for these and other constancy effects. Size and shape constancy, in particular, have been shown to vary considerably with the instructions given to the observer or with the 'set' he adopts in looking at the scene.

ROLE OF INSTRUCTION AND EXPERIMENTAL SETTING. The relative success of explicit instruction or deliberately adopted attitudes (159) in diminishing constancies probably differs for different constancy effects: loudness judgments for speech (at varying distances) show nearly complete constancy, in spite of instructions to judge the loudness 'at the ear,' and not 'at the source' (350); for pure tones or noise, loudness constancy is considerably less. Even for the latter stimuli, constancy increases if the intervals between standard and comparison sounds are prolonged, just as visual size constancy seems favored when the angular separation of standard and variable object is increased (243).

EFFECTS OF 'REDUCTION.' The simplest, yet most effective way of diminishing constancy effects is the use of the 'reduction screen' (249, 251) or of equivalent procedures. The use of reduction can be shown, for instance, in the experiments on brightness constancy introduced by Katz (249); two color mixers (wheels with adjustable black and white sectors) are placed side by side, separated by a shadow-caster. If an observer is asked to adjust the black-white mixture of the illuminated color wheel so that it matches the brightness of the shaded wheel, he will add some black to obtain a match but not as much by far as would be required by the (lower) photometric luminance of the shaded wheel. If he now looks at each of the wheels through a 'reduction screen' (an opaque screen with a hole), the match breaks down and the gray of the shaded wheel looks much darker than that of the illuminated one. Reduction can be accomplished similarly by removing accessory objects from the field of view, by monocular observation, or, as we have seen, by photography.

The famous size illusion in Ames' distorted room (8, 236; see fig. 32) is in fact a special instance of destruction of size constancy under conditions of extreme 'reduction'; the actual room is not rectangular but shaped so that the far wall slants away to the left. As a result, the window at the left is at a greater distance than that on the right. To obtain the illusion of a discrepancy in the size of the heads appearing in the two windows, the observer must see no microstructure (which would yield a gradient on the far wall), must use only one eye and must avoid eye or head movements. The same 'reduction' is of course accomplished by photographing the room; hence the fact that the illusion is obtained in the photograph

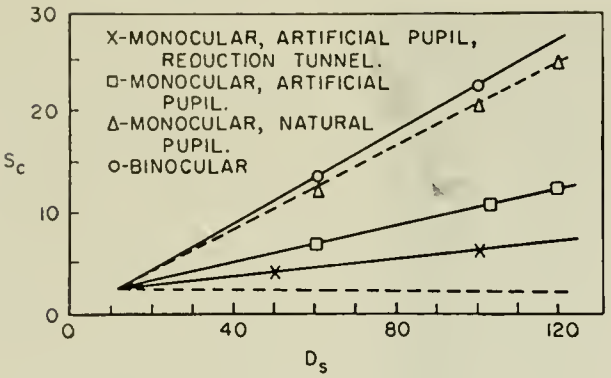



FIG. 33. Effects of 'reduction' on apparent size, summarizing experimental results of Holway & Boring (220). The *ordinate*, $S_c$, gives the diameter in inches of the comparison stimulus equated in apparent size to the diameter of a standard stimulus (subtending 1°). The comparison stimulus is kept at 10 ft. from the observer. *Abscissa* values indicate the various distances in feet from the observer at which the standard stimulus was placed. The *oblique broken line* defines the locus of all results obeying the 'law of size constancy'; the *horizontal broken line*, all results obeying the law of the visual angle. There was slight 'overconstancy' on free binocular regard, but progressively less constancy as increasingly severe conditions of 'reduction' were imposed. [Modified from Holway & Boring (220).]

of the experimental arrangement. Moving one's eye while looking at the (real) distorted room, or moving one's hand with a stick through the room, touching various parts, leads to a perception of the slant, and a 'correct' (undistorted) view of the heads.

The most systematic study of 'reduction' in its effect on size constancy is that by Holway & Boring (220). They measured the apparent size of a standard disk (subtending a visual angle of one degree) as the distance of the standard was varied from 10 to 120 ft. in a long corridor. The functions relating apparent size to distance were obtained under free binocular viewing conditions; these functions showed nearly complete constancy (see fig. 33). The measurements were then repeated under conditions that, in the opinion of Holway & Boring (220), represented a serial reduction of size perception, viz. *a*) under monocular regard; *b*) monocular, with small artificial pupil; and *c*) monocular, with artificial pupil and a long black reduction tunnel. As the reductions increased, the constancy effect declined and approached (for condition *c*) the 'law of retinal image size' (or visual angle).

In discussing these results, the authors point out that constancy (e.g. of size) is in most cases a hyperbolic expression. [Helson (196) making the same point, suggested we substitute the term 'compensation.'] Alley trees do converge towards the horizon (as do railroad tracks), although we can also see that they are equidistant. Can we see both at once, or do we see convergence and equidistance in alternation, 'at will,' depending on our attitude (55)? Perhaps we do see both but say two things when we stop to talk about it; immediate perception, even in the normal state, has these elements of 'unreasonableness' that loom so much larger in the spectacle experiments [see above (285)]. To paraphrase an earlier statement, if perception did not have certain non-geometric (or, at least non-Euclidean features), the discovery of geometry by Euclid and his predecessors would have been less of an invention.[30] If maximal reduction as in the Holway-Boring experiment throws the perceiver back upon a perspective mode of seeing (155), this does not mean that this mode is more 'basic' than the normal multidetermined mode of perceiving. It is probable that there is no reduction radical enough to abolish simultaneously all constancies without abolishing pattern, depth and motion, i.e. without rendering size and distance indeterminate.

### *Loss of Constancies After Cerebral Lesions*

Such a condition is probably realized after total destruction of the primary projection system. After bilateral occipital lobectomy, monkeys react to light, in fact, as if there were no constancies, but merely luminous flux (261). As Klüver (261) points out, this residual visual capacity must not be described as a preservation of perception of 'brightness' in the absence of all patterning, since brightness implies ability to react to flux per unit area, regardless of wide variations in the area on which the brightness appears, its shape or its distance. Thus, the monkey with bilateral occipital lesions can be trained to

[30] Lüneburg (330) has, in fact, attempted to describe perceived (binocular) space as non-Euclidean. Lüneburg devised a three-dimensional bipolar coordinate system to encompass the results of Hillebrand's (213) and Blumenfeld's (49) famous alley experiments; apparent parallel alleys (of luminous dots in a dark room) are physically narrower than alleys set to appear of the same width. By fitting this peculiar situation into a non-Euclidean (hyperbolic) space (in which the parallel axiom does not hold), Lüneburg hoped to derive a general metric of binocular space where size constancy would follow from its particular geometry. Empirical tests of Lüneburg's approach have yielded somewhat discordant results (179, 427, 428).

choose the 'brighter' of two targets of equal size and will then immediately transfer this choice to the larger of two targets differing in size but equal in brightness. Similarly, moving one of two identical targets further away, or interrupting its illumination, say, once per second, will make this target equivalent to a dimmer one. By such applications of converging operations (method of equivalent-nonequivalent stimuli) Klüver was able to demonstrate the unusual character of the visual world of the monkey with occipital lesions, a mode of reacting never found in the normal animal who perforce reacts to interdependent dimensions in his visual field—'shape' in spite of varying orientations, 'size' with varying distance, 'brightness' with varying size, etc. (259).[31]

A corresponding state has been observed, at least transiently, in man after massive occipital lesions. The initial effect of large subtotal lesions of the geniculostriate system in man is usually complete blindness which recedes in minutes, days or (rarely) weeks (386, 469). This recovery takes place in stages, so that different aspects of perception return in a regular sequence. First to recover is an undifferentiated sensation of light [a reaction to total flux (261)] without shape, color or localization in space. After that, movement of a light may be distinguished from a stationary light, but the patient is still unable to indicate direction or speed of the movement, and thresholds for detection of movement are elevated. Still later, localization of objects in visual space becomes possible, although with abnormal errors and often with systematic distortions in the subjective coordinates of perceptual space [see Fuchs (136) and Teuber & Bender (473)]. At this stage, contours are described as 'fuzzy' and unstable, and color is usually absent. Finally, contours take on a normal appearance, and color experiences become possible (often after a period of intense red coloration of the entire field—erythropsia). There are also reports of a definite sequence in the recovery of different colors [see Lhermitte & Ajuriaguerra (321)]. At no stage, however, is there a selective loss of constancies; they are absent only in the absence of perception of pattern, depth and motion with which they are indissolubly linked.

[31] It should be noted that the extreme periphery of the normal visual field of man also exhibits reactions to visual flux, as proved by Gross & Weiskrantz (173). This observation does not detract from the ingenuity of Klüver's analysis (on which it is based) but suggests that experiments on monkeys should be repeated with further histologic controls to rule out any possible escape of the most anterior parts of the striate cortex. These regions, in the depth of the calcarine fissure, probably represent the most peripheral portions of the visual field, in man as well as in monkey.

*Deprivation and Recombination Studies*

If constancies as such are only abolished by total destruction of projection systems, then one must turn to evidence from isolation or rearrangement studies in order to search for possible physiologic correlates. Some constancies, e.g. those of perceived velocity or visual direction, are clearly impaired during and after the wearing of inverting or distorting spectacles (285, 286), or by short-term periods of sensory deprivation (40, 205). Whether this is equally true of other constancies, e.g. those of perceived color or brightness, is not yet known. 'Loss' of color constancy in spectacle experiments is made unlikely by the observation that the colored fringes induced around borders in the field on wearing prismatic spectacles tend to disappear with time, only to reappear briefly (and in reverse orientation) when the prisms are removed. A remarkable form of this effect is Kohler's observation (285) with bipartite red-and-green glasses, so worn that the left half of each monocular field is green and the right half, red. On turning the eyes to the right, the observer sees the world tinted in red; with eyes turned to the left, the world turns green. After several days of continued wearing of these glasses, the color effects disappear, but reappear in opposite fashion when the glasses are taken off; now the world looks green on turning the eyes to the right, and red on turning them to the left. These effects are thus specific, not for particular areas of the visual field (as would be ordinary forms of adaptation), but specific for particular ocular postures. The results, if confirmed, would go beyond any predictions derived from Hering's or Helson's approach to chromatic adaptation and color constancy. Kohler himself (285) speaks of 'conditional sensations,' i.e. particular sensations that have become associated with particular movements and postures. These radical antichromatic responses (184), although irreconciled with any current approach to perception, may have parallels in other and better-known phenomena.

The moon-illusion, for instance, has been noticed and discussed since antiquity. Moon and constellations look large near the horizon and smaller near the zenith. Artificial moons in a laboratory sky behave analogously (416). The thorough analysis of the phenomenon by Boring (54) revealed that the neces-

sary and sufficient condition for having the moon 'shrink' at the zenith was elevation of regard, a size-impression conditional upon a particular posture of the eyes in the orbits. Not only direction of gaze, but changes in accommodation can condition apparent size [although accommodation is demonstrably not the sole determinant of size constancy (504)]. This need not mean that we integrate some proprioceptive feedback from eye muscles with the visual impression received; what may matter here again is the efferent activity in its influence on the sensory system.

Consider the micropsiae and macropsiae induced by drugs. If one instills atropine into the eye, thus paralyzing accommodation, the lens is permanently accommodated for distance. If one looks at a landscape and tries to accommodate (unsuccessfully, because of the paralysis) onto a near object (say, one's finger), the distant landscape shrinks (micropsia). The opposite effect can be obtained by instilling physostigmine into the eye, inducing a spasm of accommodation. The lens is then permanently accommodated for near objects. Attempts at accommodation onto distant objects lead to marked macropsia; the distant landscape expands. These forms of micropsia and macropsia can perhaps be understood if one considers what happens as long as accommodation is normal. As objects approach, two continuous and concomitant changes occur; accommodation increases, and so does the visual angle subtended by the object. Perceptually, however, the object stays approximately the same size. One can assume, as we have several times before, that this constancy is the result of a central counteraction which 'shrinks' the approaching object in keeping with increasing accommodation. Such regulatory feedback need not go via the periphery; a corollary discharge from the central oculomotor system into the visual system could be conceived as the source of such a 'physiologic micropsia' for approaching objects, and of the relative macropsia for receding ones. The notion which has already been developed in some detail by von Holst (504) is schematized in figure 31. The same principles have been used in Mittelstaedt's analysis (348) of prey capture in mantids.

It is clear that on these notions many illusions (such as micropsia and macropsia) are really constancies misapplied.[32] One of the simpler (and earlier) examples for this relation is Emmert's 'law' (52, 112) which states that an afterimage increases with the (perceived) distance of the surface on which the observer projects it. If our theoretical approach to size constancy is valid, then the increasing apparent size of afterimages, at increasing projection distances, is such an instance of size constancy running off *in vacuo*. The 'retinal size' of the afterimage does not change, once established; it is just for that reason that the perceived size of the afterimage is subjected to the (centrally guided) expansion with increasing distance. For a normal object, this expansion in size would counteract the diminution in visual angle as the object recedes. Convergence and accommodation are among the principal determinants here of afterimage size. Some observers, however, report the same effect while projecting an afterimage into increasingly 'distant' recesses on the perspective drawing of a tunnel.

### *Illusions: Phenomena and Interpretations*

ILLUSIONS AS MISAPPLIED CONSTANCY EFFECTS. The famous optic-geometric illusions, as we have seen (above, p. 1601), have been a major concern of the nineteenth-century students of perception (53), the interest waning somewhat (though never completely) with the insight into the inappropriateness of separating these illusions from other perceptual phenomena. Two major types of illusions were distinguished, those involving visual extents, and those involving angles, although many patterns were devised incorporating both angular and linear distortions in one and the same figure. One of the earlier illusions of extent was Oppel's demonstration (368) in 1855 that interrupted lines are overestimated in comparison with uninterrupted ones (fig. 34, upper left). Soon afterwards in 1858, Wundt (550) pointed out that vertical lines tend to be overestimated in comparison with horizontal lines, as shown in figure 34. von Helmholtz (501) combined both effects that of vertical-horizontal, and of inter-

[32] Analogous considerations apply to more complex forms of illusions such as the size-weight illusion (75, 76). In this familiar illusion, a large (but hollow) object is judged as much lighter (upon hefting) than it would be if the identical weight were presented in the form of a less bulky (but more massive) object. Presumably we 'expect' objects to show increasing weights with increasing size; in holding out a hand to receive a weight or to lift it, we are 'set' in different fashions, depending on the anticipated weight. Unless there are unanticipated disproportions between the actual density and the visual appearance of a weight, our motor readiness will be appropriate. In fact, there are marked (though relatively unexplored) constancies for weights, e.g. we ordinarily compensate, in part, for differences in lever-action, as when the same weight is applied to more proximal or more distal parts of a limb (124, 250).

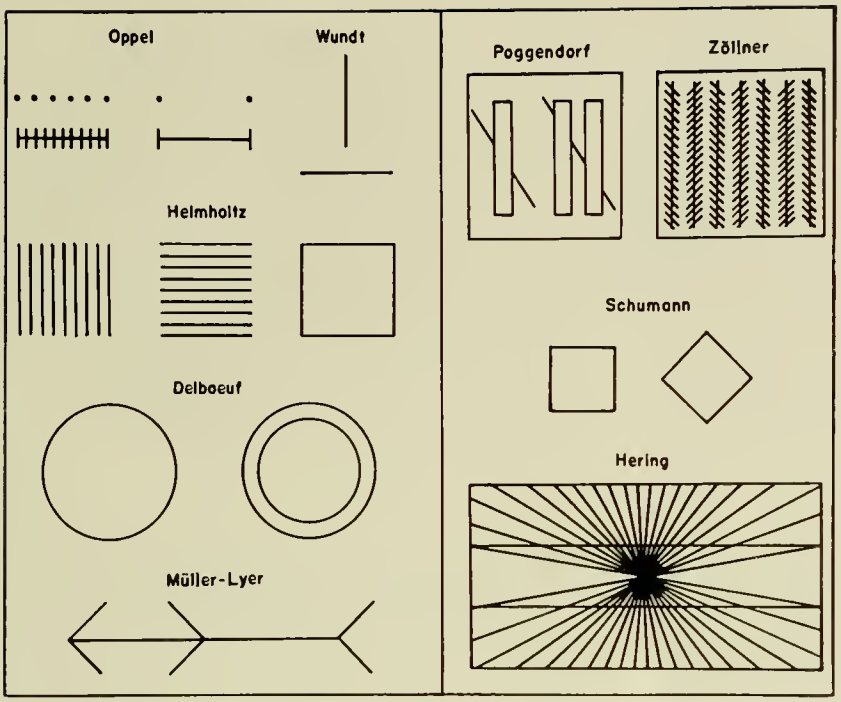



FIG. 34. Some of the classical optic-geometric illusions. In the *left section*, so-called illusions of extent; in the *right section*, illusions of angles. Both extent and angle are affected simultaneously in several of these patterns, e.g. in the Müller-Lyer illusion (*lower left*), and in Schumann's upright and rotated squares (*middle right*).

rupted vs. uninterrupted extents in his squares (fig. 34). The most famous illusions of extent, however, are the circle illusions of Delboeuf (98), an illusion of area (fig. 34), and the Müller-Lyer 'paradox' (355) in which the length of a line is over- or underestimated, depending on the angle formed by the 'wings'; where these wings form acute angles with the main line, the line is underestimated; where the angles formed are obtuse, the line is overestimated (fig. 34, lower left).

Illusions involving angles are just as diverse as those of extent, beginning in 1860 with the Poggendorff and Zöllner figures, both reported by Zöllner (559) in 1860 [although Poggendorff's figure was not named for him until much later (79)]. There were many variants of these effects, such as Hering's figure (199) and the numerous illusions of 'shape' in which a simple geometric form appears distorted on superposition on various repetitively patterned backgrounds, as shown in figure 35 (370).

The numerous theories that have been introduced from time to time to account for these illusions have been reviewed by Boring (53) and by Woodworth & Schlosberg (549). Most of the theories are *ad hoc*, and only one, the recent approach by Piaget (376), is quantitative. Piaget's theory, however, seems to us contradicted by the observation by Pritchard (389) that the major classes of optic-geometric illusions keep their effects when viewed with complete stabilization of the retinal image. Of great interest, however, is the recurrent notion that most or all of the illusions are, in fact, tendencies towards size or shape constancy that are misapplied (462, 504), or the broader but equivalent view that the illusory patterns present atypical 'rigged' environments to which the perceiver adapts as he does to dioptrically induced distortions of his input (Held, unpublished observations).

In a recent formulation of this view by Tausch (462), illusions of extent and angles are derived from size and shape constancy, as shown in figures 36 and 37. In the ordinary view of a rectangular table (seen from the front), the far edge has to be 'enlarged' in perception to maintain constancy of size and the angles 'rectified'; the angles close by have to be made less acute and the distant angles less obtuse to approach rectangularity. To a perspective drawing of such a table, the same rectification tendencies are applied and the tendencies persist, even when relatively isolated lines and angles are exhibited on paper. The process involved would resemble the 'release' of particular behavioral tendencies by schematized or fragmentary dummy-stimuli, as demonstrated in ethological studies of animal perception [e.g. Tinbergen (486)]. The railroad tracks that converge as they stretch toward the horizon would present another original situation that is schematized in a standard

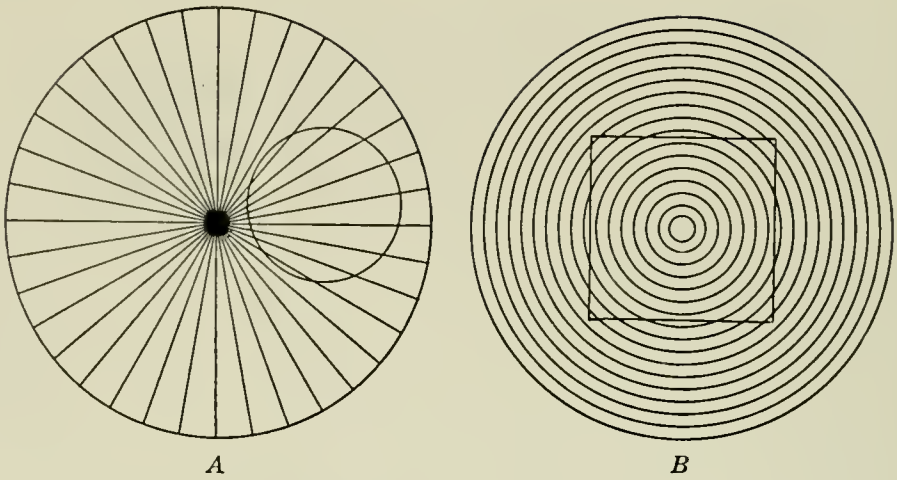



FIG. 35. Orbison's patterns. The regularly patterned backgrounds induce systematic and predictable distortions in the line patterns (perfect circle in *A*, perfect square in *B*) that have been superimposed on these special backgrounds. [After Orbison (370).]

illusion, viz. of Ponzo's design (shown in fig. 36) where two or more lines are seen to converge; figures inscribed in those regions where the converging lines approach each other are overestimated. The illusion here would be due to a normal tendency to see more distant tracks as larger than their geometrical projection. In fact, Tausch (462) has attempted to find, for every illusion, a corresponding prototypical constancy in real life (fig. 37).

This approach is particularly attractive because it would account, if true, for the curious anisotropies of apparent extents in the visual field. In a normal (monocular) field of vision, targets of equal visual angle appear relatively smaller to indirect (peripheral) gaze, as compared with direct fixation; they also seem smaller in temporal and lower portions of the field. These asymmetries can be demonstrated quantitatively on monocular bisection of lines; the nasal (and upper) portions are usually made shorter than the temporal (or lower) portions, since the latter 'look smaller.'[33] Such results imply a relative micropsia of temporal and of lower halves of the visual field, and relative macropsia of nasal and upper halves. According to the views just developed, these physiologic micropsiae and macropsiae are understandable. Normally, objects in the nasal and upper parts subtend smaller visual angles, since they are near the vanishing point, and constancy of size would therefore tend to enlarge these objects. As the moon illusion shows, however, this effect is not restricted to retinal areas, but is also associated with particular positions of the eyes; the moon is maximally enlarged as we look toward the horizon and it 'shrinks' on elevation (as well as deflection) of binocular regard.

PERCEPTUAL HABITUATION; DECREMENT OF THE MÜLLER-LYER ILLUSION ON REPEATED TRIALS. The Müller-Lyer effect and those induced by similar patterns (Poggendorff, Zöllner) diminish on repeated exposure (244). Particularly when trials are massed [rather than distributed over longer periods (353)], an observer will set the two segments of the pattern with decreasing 'errors,' sometimes to the point where the illusion disappears and gives way to a slight effect in the opposite direction. This decrement of the illusion on repeated trials occurs in the absence of any knowledge of results, and thus differs from ordinary forms of learning (276). In this respect, the decrement is quite analogous to the progressive diminution in the errors of localization induced by prisms (194) or pseudophones (192). The decrement of the Müller-Lyer effect disappears when trials are resumed after the pattern has been turned around end to end. Köhler & Fishback (276) propose therefore that the decrement should be subsumed under the paradigm of those figural aftereffects which are specific for certain positions in the visual field. In all these respects, the decrement resembles the phenomenon of specific habituation to originally arousing stimuli described by Sharpless & Jasper (424) [see also Sokolov (432)].

INTERMODAL TRANSFER OF MÜLLER-LYER DECREMENT; 'HAPTIC' ILLUSIONS. It can also be shown that the decrement takes place for a tactile analogue of the Müller-Lyer pattern (Rudel, unpublished observa-

[33] Brown (69) has shown that such meridional asymmetries are somewhat unstable; they change progressively on prolonged testing, especially if trials extend over several days.

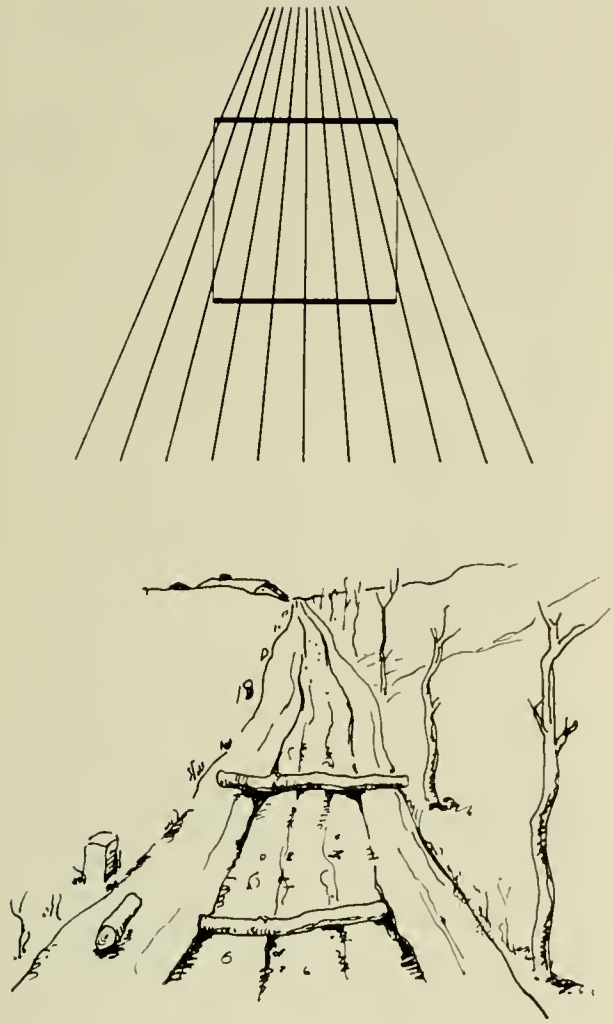


FIG. 36. The Ponzo illusion (above) as an inappropriate constancy effect. The *distant log* lying across the path in the scene *below* is actually of the same length as the *one* parallel to it which lies in *front*. If perspective is taken into account, the *more distant log* seems much larger. However, the illusion is effective in observers who are shown the drawing in 180° rotation and are thus unaware of its meaning; the elongation of the line crossing the denser gradient of converging lines seems therefore essentially like the effects illustrated in fig. 35. [Modified from Ponzo (385) and von Holst (504).]

tions); once established, the decrement is transferred (at least in part) to the visual form. Strangely, however, there is less transfer in the reverse direction, i.e. after massed visual trials to subsequent tactile presentations. This curious asymmetry of intermodal transfer is still unexplained.

Haptic analogues exist for most of the optic-geometric illusions (398). They are sometimes dismissed as results of transfer from the visual to the haptic (i.e. tactile-kinesthetic) situation, but this interpretation is called into question by the fact that congenitally blind children obtain strong haptic illusion effects, e.g. on presentation of the Müller-Lyer pattern in relief. These observations create various difficulties for the ingenious approach to the visual illusions proposed by Tausch (462) and von Holst (504).

FIGURAL AFTEREFFECTS. The findings on the congenitally blind favor the argument (276) that some illusions at least, and their decrement on prolonged inspection, can be treated as instances of figural aftereffects (271, 281). We have already dealt with the related earlier observations on slow diminution of apparent curvature for straight lines that had been made to appear curved by a prism (151, 552). Gibson (151–153, 158) has studied these changes in detail, showing that they occurred, without the use of prisms, on mere inspection of curved or tilted lines, and that there were measurable aftereffects, in which objectively straight lines appeared curved or tilted in an opposite direction. He also showed that these effects had a tactile-kinesthetic counterpart; on rub-

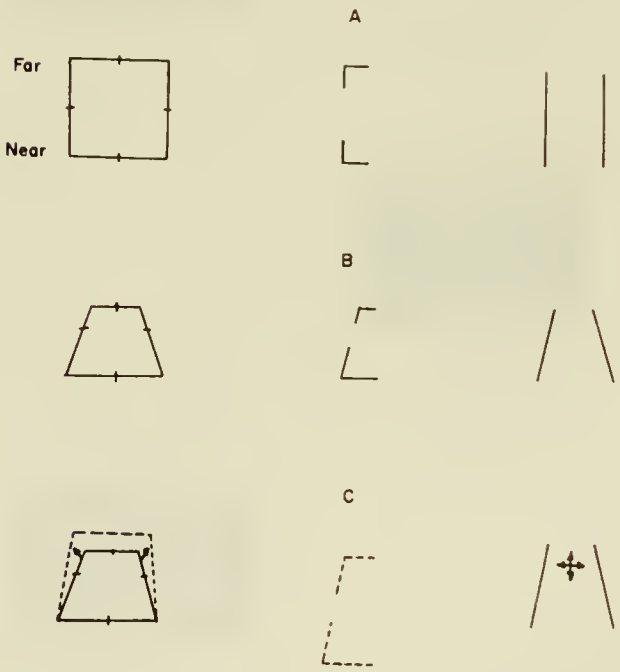



FIG. 37. Illusions as misapplied constancies. *A*: The appearance of a square surface (e.g. a table top) seen from in front and slightly from above is distorted by the laws of geometrical optics as shown in *B*. The perceptual process is thought to operate upon this pattern by counterdistortion, resulting in the changes schematized in *C*. Such a process would involve apparent lengths, sizes and angles. [Modified from Tausch (462).]

bing one's hand along a curved edge, the apparent curvature gradually diminishes. If one then rubs one's hand along an objectively straight edge, the latter seems curved in the opposite sense.

Köhler (271) believed that all these effects might be closely related to some central process of 'satiation' which he felt caused the apparent reversals on prolonged inspection of an ambiguous pattern (e.g. the Necker cube; see fig. 40). Subsequently, Köhler & Wallach (281) subjected the visual forms of figural aftereffects to a detailed investigation. A paradigmatic experiment is illustrated in figure 38. Prolonged fixation of an inspection pattern, *I* (which may be any kind of stable contour in the visual field), induces predictable changes in the appearance of a test pattern, *T*, that is subsequently viewed. In essence, any contour presented at a short distance from the retinal

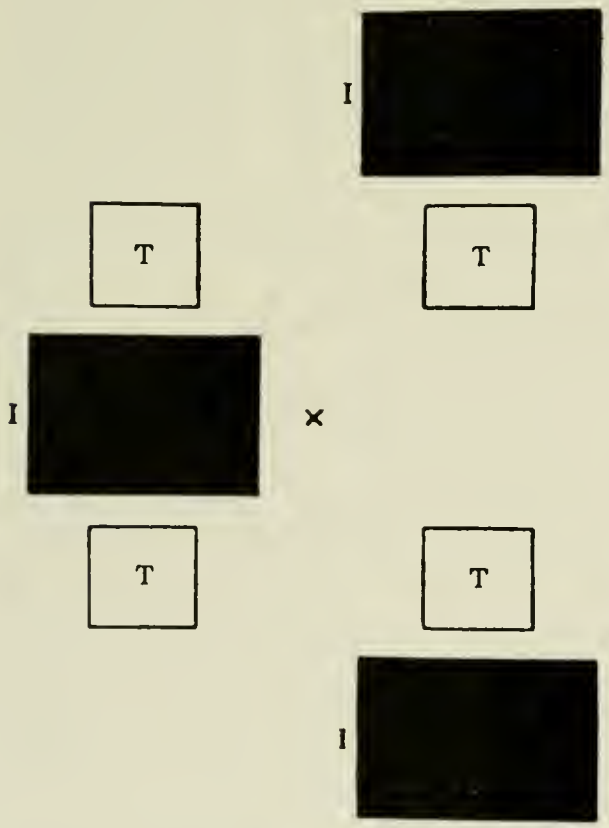



FIG. 38. Figures used by Köhler & Wallach to induce figural aftereffects. Following inspection of the pattern marked *I* (the solid black rectangles), a subsequently exposed test pattern, *T* (the four outline squares) appears temporarily altered, the two squares on the left seem to have moved further apart, the two on the right, closer together. Fixation is maintained throughout at *X*. [From Köhler & Wallach (281).]

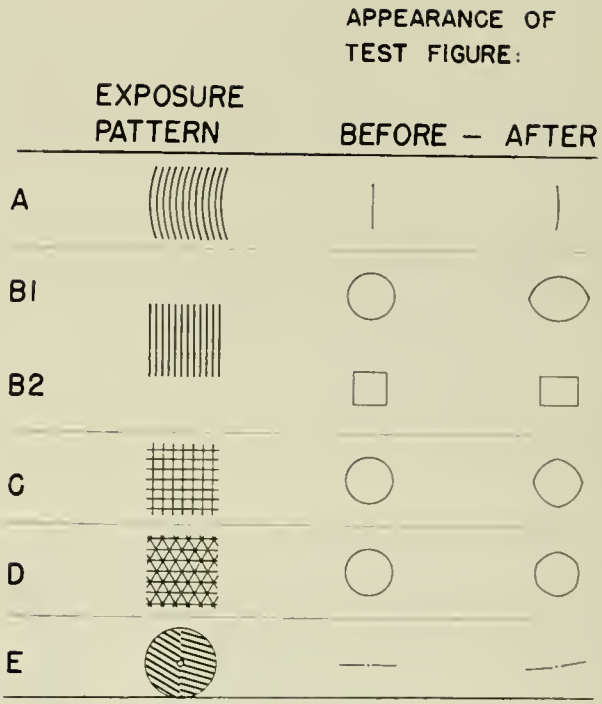



FIG. 39. Aftereffects induced by active scanning of various patterned fields. *A*: Scanning the set of *curved lines* for 1 min. induces apparent curvature in an objectively straight line; the *curved line* shown at *right* is now called straight. Analogous transformations are shown under *B–E*. Scanning the set of *vertical lines* for 1 min. induces horizontal elongation and distortion of circles (*B1*) and converts squares into rectangles (*B2*). *C* and *D*: *Checkered fields* convert circles into polygons. *E*: Scanning for 1 min. within the circle converts a horizontal line as shown. In a sense, the bias induced by the special exposure fields sets up new equivalence classes; polygons are now circles, etc. For similar interpretations see Taylor & Papert (463). [Adapted from Held (unpublished observations).]

region of the previously inspected contour appears to be displaced away from that region. With increasing separation of *I* and *T* lines, these apparent displacements increase to a maximum and then decrease [the 'distance paradox' of Köhler & Wallach (281)].

In their physiologic theory of these figural aftereffects, Köhler and Wallach assumed that satiation builds up during prolonged inspection of contours as a slow polarization in primary projection fields (271, 273, 281). Actual measurements of d.c. potential changes from occipital (277, 278, 280) and other regions (279, 282) are adduced in support of the theory in which cortical potential gradients and their configurations in a volume conductor form the representations of perceived distance and shape. As Lashley has pointed out (308), the theory is unique

in its boldness and simplicity. The invocation of graded potentials is much more defensible at present than it might have seemed at the time the theory was first proposed. Nevertheless, Lashley (308) and others have stressed a number of difficulties with the theory, the only one so far "that has ever predicted correctly" any perceptual fact.

First, effects of lesions in the primary projection fields would seem to speak against the theory in its present form. Illusions and constancies are preserved in small remnants of a visual field; motion and patterns are perceived across scotomata (see above). Crisscrossing the visual cortex in cats and monkeys with knife cuts, or implanting multiple pieces of gold foil (309, 442) or mica plates (441) into the structure, produce no disturbance of pattern vision that is demonstrable with the tests employed. Even the passage of currents into the occiput of human observers who were engaged in various visual tasks (482) has thus far produced no measurable change not even in such delicate phenomena as the spontaneous fluctuations of reversible figures.

The theory, as Köhler himself points out, is restricted. It is difficult to apply to the tactile-kinesthetic forms of aftereffects (274), or to the visual aftereffects involving displacement of test patterns in the third dimension (275). [There may be less difficulty in applying the theory to auditory aftereffects (102, 290)]. The greatest restriction of the theory, however, flows from the simple fact that most of the aftereffects described can be obtained with freely moving gaze (Held, unpublished observations). Active scanning of the various patterned fields shown in figure 39 induces systematic changes in subsequent perception (97; Held, unpublished observations; see also 410). These observations do not fit the present concept of isomorphism [nor, for that matter, the alternative theory of aftereffects proposed by Osgood & Heyer (371) and based on the earlier work of Marshall & Talbot (340)]. The aftereffects of inspecting especially patterned fields with moving gaze seem to be closely connected with those set up by prisms or pseudophones; a successful theory would eventually have to comprise both sets of phenomena, the figural aftereffects and the adaptation to distorting media.[34]

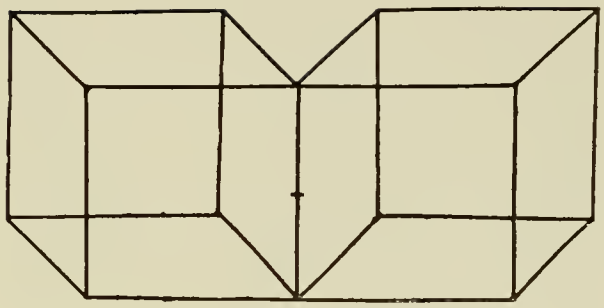


FIG. 40. Double Necker cube. On continued fixation at the small horizontal *cross-bar* in the center, the two cubes fluctuate 'spontaneously,' reversing their perspective, often in synchrony, sometimes asynchronously. [From Cohen (90).]

It would be particularly helpful if we knew whether cortical lesions influence either of these phenomena in some systematic fashion.[35] Unfortunately, information on this point is scant and contradictory (443). Increased susceptibility to tactile-kinesthetic aftereffects in brain-injured men has been claimed (256) and denied (237). By contrast, reversal rates for ambiguous patterns are known to be influenced by brain injury (90, 182), but the alterations are difficult to interpret in the absence of information on related perceptual phenomena.

In the most complete study of figure reversals after brain injury, reversal rates were found to be decreased after unilateral lesions in any cerebral lobe [see Cohen (90)], although this decrease was greater with right than with left hemisphere lesion (see fig. 40, 41). Bilateral lesions in the posterior brain substance diminished reversals even further, but bilateral frontal lesions had a paradoxical effect (fig. 41). After this injury, there was marked and persistent enhancement in reversals for the ambiguous pattern, so that bifrontal cases differed from normal controls by showing 'too many' reversals, and unilateral frontals, by showing 'too few' (fig. 41). The sensitivity of this simple perceptual task to brain injuries of varying sites is remarkable, but the inter-

[34] It would be desirable in this connection to determine whether lower species, e.g. fish, show habituation (i.e. decrements) to the Müller-Lyer pattern. Fish are subject to these geometric illusions as much as man, and perhaps more, as proved by Herter (206). For birds (domestic chicks) there are similar data on strong effects of certain optic-geometric illusions (397). For the lemur (an arboreal primate), however, von Allesch (494) reports a 'reversal' of the vertical-horizontal illusion, so that this monkey, in contrast to man, overestimates horizontal rather than vertical extents.

[35] Köhler and his associates (273, 276) have noted that the transient effects of visual 'satiation' in normal fields tend to resemble some of the persistent changes after occipital lesions in man. In both conditions there is rapid fading of contours, reduced fusion thresholds for flicker and changes in motion perception, and there are displacements and recessions of objects in perceptual space.

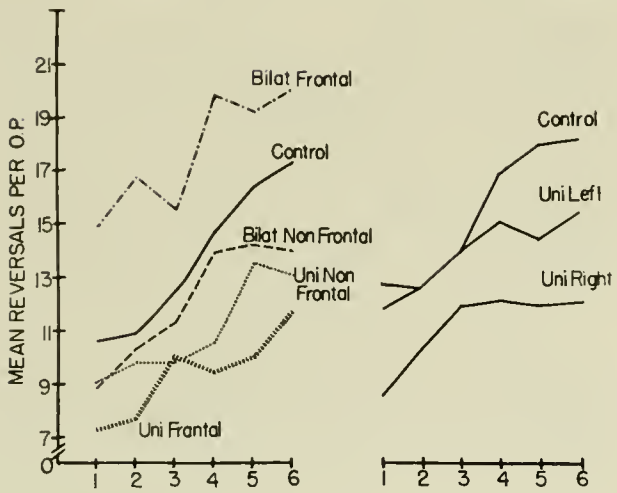



FIG. 41. Reversals of the Necker cube shown in figure 40 as a function of brain injury. Average number of reversals (*ordinate*) are plotted for each of six successive 15-sec. observation periods (*abscissae*). Normal adults (*controls*) show reversal rates which increase up to the middle of the total 1½ min.-period and then level off. Patients with unilateral frontal lesions show fewer reversals than those with lesions elsewhere in the brain (unilateral or bilateral nonfrontal brain lesions). Patients with unilateral lesions of the right hemisphere show fewer reversals than those with unilateral lesions of the left hemisphere. Patients with bilateral frontal lesions (*upper left*), however, show significantly higher reversal rates than controls and all other groups with brain injury. [From Cohen (90).]

pretation of the changes observed will continue to elude us, until we are able to devise a more adequate perceptual theory (91).

## CONCLUSION

The forms that a theory of perception may have to take can perhaps be sketched. The theory would have to deal with the basic facts of perception that have recurred in this review: responses to patterned fields, to gradients and ratios of stimulation, transposition of patterns (and its limits), and orderly response to sequentially patterned stimuli. There is little hope of understanding the underlying processes if we continue to restrict investigation to such unnatural stimuli as single points of light, pure tones (or even clicks) and punctate pressure. No man-made analogue of the nervous system would be able to start with such sensations and arrive at the perceptions of which so many species seem to be capable.

Nor can we expect to understand the essential central correlates of perceiving by adhering to those conceptions of the nervous system which view it as a passive receiver of sensory information. The nervous system must operate upon its inputs, not only by selecting them, but by providing the essential 'constancies' without which the information would be chaotic. Neither field theories [such as that of Köhler (273)], nor scanning theories of perception can thus far deal with these problems. The field theory has difficulties (which we have described) and disregards much of the intricacy and orderliness of the neural substrate. The scanning notions were specifically devised to deal with perceptual constancies [see Pitts & McCulloch (381), Deutsch (103) and Sutherland (461)], but they too conflict with facts [e.g. MacKay (334) and Teuber *et al.* (469)], and none can explain even the limited readjustment of constancies as seen in rearrangement experiments.

Throughout this chapter we have stressed the potential role of a central corollary discharge which is postulated as coordinating efferent and afferent processes. This corollary discharge presumably travels from motor into sensory systems at the onset of every bodily movement and thus permits anticipatory adjustment of the perceptual process. These discharges are pure conjecture; if they exist, they would enable the organism to distinguish ordinary afferent stimulation (due to changes in the environment) from reafferent stimulation due to his self-produced movements. If modifiable (in higher species), these corollary discharges might serve as carriers of perceptual adaptation to altered sensory environments; they can, as we have shown, account for certain illusions, and they may be important in building up classes of responses to equivalent stimuli in a normally patterned environment. Malfunctioning of this internal activity would be evident in highly redundant (336), or in 'empty' or noisy environments (as in isolation and deprivation studies), and in some of the strange but patterned abnormalities of perception after cerebral lesions.

These fragmentary notions may raise the hope for a theory, but they are far from constituting one. It can be seen that these concepts are closely related to the earlier neurologic postulates of 'schemata' as the neural basis for awareness of posture and spatial orientation advanced by Pick (378, 379), Head (186), Lhermitte (320) and Oldfield & Zangwill (366, 367). These neural schemata appear in a new and different guise in MacKay's concept of the matching responses within the nervous system (335). The central correlates of perception may turn out to be activities that organize "an outwardly directed internal match-

ing response" to signals from the receptors (335). Such activity would amount logically to an internal representation of those features in the profusion of incoming signals to which the nervous system is adapted—either by virtue of its intrinsic organization, or as the result of more recent exposures to the environment. Probably, as we have seen, both intrinsic and acquired tendencies interact, particularly in man. In the visual system, for instance, we would conceive of internal activity as organized "to match (in a sense, to cancel out, actively) the incoming visual signals" (335, p. 41).

At the present stage, this match-mismatch hypothesis remains necessarily vague. It may seem premature to introduce it into the study of perception, but it might serve as a schema for one's own organization of the problems of perception, and the role of perceiving in complex coordinated behavior. These questions take us a hopeless distance beyond the known mechanisms of individual neurons, yet problems of patterning in behavior are identical with those of neuronal interaction. After speaking of single neurons, Adrian said (1, p. 93) "their behaviour in the mass is quite another story, but this is for future work to decide." Perception, like coordinated movement, would seem to be part of that 'other story.' It should be possible to tell all of it, if perceptual and neurophysiologic studies continue to converge.

## REFERENCES


1. Adrian, E. D. *The Mechanism of Nervous Action*. Philadelphia: Univ. Penna. Press, 1932.
2. Aggazzotti, A. *Arch. fisiol.* 9: 523, 1911.
3. Aguilonius, F. *Opticorum libri sex* II: 146, 1613.
4. Akishige, Y. *J. Fac. Litt., Kyushu Univ.* IV: 23, 1937.
5. Allport, F. *Theories of Perception and the Concept of Structure*. New York: Wiley, 1955.
6. Ames, A., Jr. *Am. J. Psychol.* 59: 333, 1946.
7. Ames, A., Jr. *Psychol. Monogr.* No. 324, 1951.
8. Ames, A., Jr. In: *Vision and Action*, edited by S. Ratner. New Brunswick: Rutgers Univ. Press, 1953.
9. Asch, S. E. and H. A. Witkin. *J. Exper. Psychol.* 38: 325, 1948.
10. Asch, S. E. and H. A. Witkin. *J. Exper. Psychol.* 38: 455, 1948.
11. Attneave, F. *Psychol. Rev.* 61: 183, 1954.
12. Attneave, F. *Am. J. Psychol.* 68: 209, 1955.
13. Aubert, H. *Arch. path. Anat.* 20: 381, 1861.
14. Aubert, H. *Arch. ges. Physiol.* 39: 347, 1886.
15. Aubert, H. *Arch. ges. Physiol.* 40: 459, 1887.
16. Axelrod, S. *Effects of Early Blindness: Performance of Blind and Sighted Children on Tactile and Auditory Tasks*. New York: Am. Fndn. for the Blind, 1959, Res. Series No. 7.
17. Balint, R. *Monatsschr. Psychiat. u. Neurol.* 25: 51, 1909.
18. Bárány, E. H. and U. Halldén. *J. Neurophysiol.* 11: 25, 1948.
19. Bárány, R. *Trab. Lab. Invest. Biol. Univ. Madrid* 22: 359, 1924.
20. Bartley, S. H. *Vision: A Study of Its Basis*. New York: Van Nostrand, 1941.
21. Bartley, S. H. *Principles of Perception*. New York: Harper, 1958.
22. Basler, A. *Arch. ges. Physiol.* 115: 582, 1906.
23. Battersby, W. S. *J. Exper. Psychol.* 42: 59, 1951.
24. Battersby, W. S. and I. H. Wagman. *Fed. Proc.* 17: 11, 1958.
25. Bay, E. *Agnosie und Funktionswandel. Eine hirnpathologische Studie*. Berlin: Springer, 1950.
26. Bay, E. *Brain* 76: 515, 1953.
27. Bender, M. and R. Jung. *Ztschr. Neurol.* 181: 193, 1948.
28. Bender, M. B. *Disorders in Perception*. Springfield: Thomas, 1952.
29. Bender, M. B. and H.-L. Teuber. *A.M.A. Arch. Neurol. & Psychiat.* 55: 511, 1946.
30. Bender, M. B. and H.-L. Teuber. *A.M.A. Arch. Neurol. & Psychiat.* 55: 627, 1946.
31. Bender, M. B. and H.-L. Teuber. *A.M.A. Arch. Neurol. & Psychiat.* 58: 721, 1947.
32. Bender, M. B. and H.-L. Teuber. *A.M.A. Arch. Neurol. & Psychiat.* 59 39, 1948.
33. Bender, M. B. and H.-L. Teuber. In: *Progress in Neurology and Psychiatry*, edited by E. A. Spiegel. New York: Grune, 1949, p. 163.
34. Beniuc, M. *Ztschr. vergleich. Physiol.* 19: 724, 1933.
35. Benussi, V. *Arch. ges. Psychol.* 29: 385, 1913.
36. Benussi, V. *Arch. ges. Psychol.* 36. 56, 1916.
37. Beritov, J. and N. Chichinadze. *Tr. Beritashvil. Physiol. Inst.* 361, 1937.
38. Berkeley, G. *An Essay Towards a New Theory of Vision* (2nd ed.). Dublin Pepyat, 1709.
39. Bevan, W., Jr. *J. Gen. Psychol.* 45: 189, 1951.
40. Bexton, W. R., W. Heron and R. H. Scott. *Canad. J. Psychol.* 8: 70, 1954.
41. Beyer, E. *Neurol. Centralbl.* 14: 10, 1895.
42. Beyrl, F. *Ztschr. Psychol.* 100: 344, 1926.
43. Bianchi, L. *Brain* 18: 497, 1895.
44. Bielschowsky, A. In: *Handbuch der Normalen und Pathologischen Physiologie*, edited by A. Bethe, G. von Bergmann, G. Embden and A. Ellinger. Berlin: Springer, 1926, vol. 12, no. 2, p. 1095.
45. Bishop, P. O. and R. Davis. *Science* 118: 241, 1953.
46. Bitterman, M. E., J. Krauskopf and J. E. Hochberg. *Am. J. Psychol.* 67: 205, 1954.
47. Bitterman, M. E. and P. Worchel. *Am. J. Psychol.* 66: 598, 1953.
48. Blackwell, H. R. and H. Schlosberg. *J. Exper. Psychol.* 33: 407, 1943.
49. Blumenfeld, W. *Ztschr. Psychol.* 65: 241, 1913.
50. Bobbitt, J. M. *J. Exper. Psychol.* 30: 273, 1942.
51. Boring, E. G. *Philos. of Sc.* 2: 236, 1935.
52. Boring, E. G. *Am. J. Psychol.* 53: 293, 1940.
53. Boring, E. G. *Sensation and Perception in the History of Experimental Psychology*. New York: Appleton, 1942.
54. Boring, E. G. *Am. J. Phys.* 11: 55, 1943.

55. Boring, E. G. *Psychol. Rev.* 59: 141, 1952.
56. Bourdon, B. *La Perception visuelle de l'espace.* Paris: Schleicher, 1906.
57. Boycott, B. B. *Pubbl. staz. zool. Napoli* 25: 67, 1954.
58. Boycott, B. B. and J. Z. Young. *Proc. Roy. Soc., London. ser. B* 143: 449, 1955.
59. Brattgård, S. O. *Acta radiol.* Suppl. 96, 1952.
60. Brecher, G. A. *Ztschr. vergleich. Physiol.* 18: 204, 1933.
61. Bridgman, P. W. *The Logic of Modern Physics.* New York: Macmillan, 1927.
62. Broadbent, D. E. *J. Exper. Psychol.* 47: 191, 1954.
63. Broadbent, D. E. *Quart. J. Exper. Psychol.* 7: 145, 1956.
64. Broadbent, D. E. *Psychol. Rev.* 64: 205, 1957.
65. Brown, D. R. *Am. J. Psychol.* 66: 199, 1953.
66. Brown, J. F. *Psychol. Forsch.* 10: 84, 1927.
67. Brown, J. F. *Psychol. Forsch.* 14: 199, 1931.
68. Brown, J. F. *Psychol. Forsch.* 14: 249, 1931.
69. Brown, K. T. *Am. J. Psychol.* 66: 629, 1953.
70. Brückner, A. *Ztschr. Augenheilk.* 38: 1, 1917.
71. Bruner, J. S. *Psychol. Rev.* 64: 123, 1957.
72. Bruns, L. *Neurol. Centralbl.* 5: 198, 1886.
73. Brunswik, E. *Wahrnehmung und Gegenstandswelt.* Leipzig: Deuticke, 1934.
74. Brunswik, E. *Psychol. Monogr.* No. 254, 1944.
75. Brunswik, E. *Systematic and Representative Design of Psychological Experiments.* Berkeley: Univ. California Press, 1947.
76. Brunswik, E. *Perception and the Representative Design of Psychological Experiments.* Berkeley: Univ. California Press, 1956.
77. Burian, H. M. *A.M.A. Arch. Ophth.* 30: 645, 1943.
78. Burkamp, W. *Ztschr. Sinnesphysiol.* 55: 133, 1923.
79. Burmester, E. *Ztschr. Psychol.* 12: 355, 1896.
80. Burtt, H. E. *J. Exper. Psychol.* 2: 63, 1917.
81. Burtt, H. E. *J. Exper. Psychol.* 2: 371, 1917.
82. Burzlaff, W. *Ztschr. Psychol.* 119: 177, 1931.
83. Buytendijk, F. J. J. *Arch. néerl. Physiol.* 2: 217, 1917.
84. Carr, H. *An Introduction to Space Perception.* New York: Longmans, 1935.
85. Carrick, R. *Tr. Roy. Entomol. Soc., London* 85: 131, 1936.
86. Carter, D. B. *J. Psychol.* 36: 299, 1953.
87. Cherry, E. C. *J. Acoust. Soc. Amer.* 25: 1975, 1953.
88. Chow, K. L. and H. W. Nissen. *J. Comp. & Physiol. Psychol.* 48: 229, 1955.
89. Clark, B. and A. Graybiel. *J. Psychol.* 28: 235, 1948.
90. Cohen, L. *A.M.A. Arch. Neurol. & Psychiat.* 81: 765, 1959.
91. Cohen, L. *Am. J. Psychol.* 72: 327, 1959.
92. Cole, J. and P. Glees. *J. Neurophysiol.* 17: 1, 1954.
93. Cott, H. B. *Adaptive Coloration in Animals.* London: Methuen, 1940.
94. Craik, K. J. W. *The Nature of Explanation.* London: Cambridge, 1943.
95. Critchley, M. *The Parietal Lobes.* Baltimore: Williams & Wilkins, 1953.
96. Crozier, W. J. and E. Wolf. *J. Gen. Physiol.* 27: 315, 1944.
97. Culbert, S. S. *J. Psychol.* 37: 81, 1954.
98. Delboeuf, J. R. L. *Acad. roy. Sc. Lettres, Beaux-Arts, Brussels* 20: 70, 1865.
99. Delboeuf, J. R. L. *Mém. Acad. Sc. Belg.* 23, No. 5, 1873.
100. DeSilva, H. R. *Brit. J. Psychol.* 19: 268, 1929.
101. Dethierage, B. H. and M. E. Bitterman. *Am. J. Psychol.* 65: 108, 1952.
102. Deutsch, J. A. *Quart. J. Exper. Psychol.* 3: 43, 1951.
103. Deutsch, J. A. *Brit. J. Psychol.* 46: 30, 1955.
104. Diamond, I. T. and W. D. Neff. *J. Neurophysiol.* 20: 300, 1957.
105. Diderot, D. *Lettre sur les aveugles, à l'usage de ceux qui voyent.* London, 1749.
106. Dimmick, F. L. and G. H. Scahill. *Am. J. Psychol.* 36: 412, 1925.
107. Ditchburn, R. W. and B. L. Ginsborg. *Nature, London* 170: 36, 1952.
108. Dodge, R. *Psychol. Bull.* 2: 193, 1905.
109. Drever, J. *Am. J. Psychol.* 68: 605, 1955.
110. Duncker, K. *Psychol. Forsch.* 12: 180, 1929.
111. Ekman, G. and B. Dahlbäck. Psychology Laboratory Reports, Stockholm University, No. 31, 1956.
112. Emmert, E. *Klin. Monatsbl. Augenh.* 19: 443, 1881.
113. Eng, H. *Ztschr. angew. Psychol.* Suppl. 39, 1927.
114. Ettlinger, G., E. Warrington and O. L. Zangwill. *Brain* 80: 335, 1957.
115. Evarts, E. V. *J. Neurophysiol.* 15: 191, 1952.
116. Ewert, P. H. *Genet. Psychol. Monogr.* 7: 177, 1930.
117. Ewert, P. H. *Psychol. Rev.* 43: 522, 1936.
118. Ewert, P. H. *Psychol. Rev.* 44: 105, 1937.
119. Exner, S. *Sitzber. Akad. Wiss. Wien, Math.-naturw. Kl. Abt. III* 72: 156, 1875.
120. Faraday, M. *J. Roy. Inst.* 1: 205, 1831.
121. Faust, C. *Nervenarzt* 18: 103, 1947.
122. Fechner, G. T. *Elemente der Psychophysik.* Leipzig: Breitkopf & Härtel, 1860.
123. Feinberg, I. *Am. J. Ophth.* 42: 473, 1956.
124. Fischel, H. *Ztschr. Psychol.* 98: 342, 1926.
125. Flechsig, P. *Neurol. Centralbl.* 13: 674, 1894.
126. Fleischl, E. *Sitzber. Akad. Wiss. Wien, Math.-naturw. Kl. Abt. III* 86: 17, 1882.
127. Flourens, M. J. P. *Recherches expérimentales sur les propriétés et les fonctions du système nerveux, dans les animaux vertébrés.* Paris: Crevot, 1824.
128. Foley, J. P. *J. Genet. Psychol.* 56: 21, 1940.
129. Forgays, D. G. and J. W. Forgays. *J. Comp. & Physiol. Psychol.* 45: 322, 1952.
130. Forgus, R. H. *J. Comp. & Physiol. Psychol.* 47: 331, 1954.
131. Frank, H. *Psychol. Forsch.* 10: 102, 1928.
132. Freud, S. *Zur Auffassung der Aphasien. Eine kritische Studie.* Leipzig: Deuticke, 1891.
133. Friedländer, M. *Ztschr. vergleich. Physiol.* 15: 193, 1931.
134. Fröhlich, F. W. *Die Empfindungszeit.* Jena: Fischer, 1929.
135. Fry, G. A. and S. H. Bartley. *Am. J. Physiol.* 112: 414, 1935.
136. Fuchs, W. *Ztschr. Psychol.* 84: 67, 1920.
137. Fuchs, W. *Ztschr. Psychol.* 86: 1, 1921.
138. Gaffron, M. *Ztschr. vergleich. Physiol.* 20: 299, 1934.
139. Galambos, R. *J. Neurophysiol.* 19: 424, 1956.
140. Galambos, R., G. Sheatz and V. G. Vernier. *Science* 123: 376, 1956.
141. Galileo, G. *Discorsi e Dimostrazioni Mathematiche Intorno a Due Nuove Scienze.* 1638.
142. Galli, A. and A. Zama. *Ztschr. Psychol.* 123: 308, 1931.
143. Garner, W. R. *J. Acoust. Soc. Am.* 26: 73, 1954.
144. Garner, W. R., H. W. Hake and C. W. Eriksen. *Psychol. Rev.* 63: 149, 1956.
145. Gelb, A. In: *Handbuch der Normalen und Pathologischen Physiologie*, edited by A. Bethe, G. von Bergmann, G.

Embden and A. Ellinger. Berlin: Springer, 1929, vol. 12, no. 1, p. 594.
146. Gellerman, L. W. *J. Genet. Psychol.* 42: 3, 1933.
147. Gellerman, L. W. *J. Genet. Psychol.* 42: 28, 1933.
148. Ghent, L. *Am. J. Psychol.* 69: 576, 1956.
149. Ghent, L., J. Semmes, S. Weinstein and H.-L. Teuber. *Am. Psychologist* 10: 408, 1955.
150. Gibson, E. J., J. J. Gibson, O. W. Smith and H. Flock. *J. Exper. Psychol.* 58: 40, 1959.
151. Gibson, J. J. *J. Exper. Psychol.* 16: 1, 1933.
152. Gibson, J. J. *J. Exper. Psychol.* 20: 553, 1937.
153. Gibson, J. J. *Psychol. Rev.* 44: 222, 1937.
154. Gibson, J. J. *The Perception of the Visual World.* Boston: Houghton, 1950.
155. Gibson, J. J. *Psychol. Rev.* 59: 149, 1952.
156. Gibson, J. J. *Psychol. Rev.* 61: 304, 1954.
157. Gibson, J. J. and E. J. Gibson. *J. Exper. Psychol.* 54: 129, 1957.
158. Gibson, J. J. and M. Radner. *J. Exper. Psychol.* 20: 453, 1937.
159. Gilinski, A. S. *Am. J. Psychol.* 68: 173, 1955.
160. Götz, W. *Ztschr. Psychol.* 99: 247, 1926.
161. Goldstein, K. *After-Effects of Brain Injuries in War.* New York: Grune, 1942.
162. Gonzalez, R. C., G. V. Gentry and M. E. Bitterman. *J. Comp. & Physiol. Psychol.* 47: 385, 1954.
163. Gordon, D. A. *Am. J. Psychol.* 60: 202, 1947.
164. Gottschaldt, K. *Psychol. Forsch.* 8: 261, 1926.
165. Gottschaldt, K. *Psychol. Forsch.* 12: 1, 1929.
166. Graham, C. H. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951.
167. Graham, C. H., K. E. Baker, M. Hecht and V. V. Lloyd. *J. Exper. Psychol.* 38: 205, 1948.
168. Granit, R. *Receptors and Sensory Perception.* New Haven: Yale Univ. Press, 1955.
169. Graybiel, A. *A.M.A. Arch. Ophth.* 48: 605, 1952.
170. Graybiel, A. and D. I. Hupp. *J. Aviation Med.* 17: 3, 1946.
171. Grether, W. F. *J. Exper. Psychol.* 30: 69, 1942.
172. Griffin, D. R. *Listening in the Dark: The Acoustic Orientation of Bats and Men.* New Haven: Yale Univ. Press, 1958.
173. Gross, C. G. and L. Weiskrantz. *Quart. J. Exper. Psychol.* 11: 49, 1959.
174. Guhl, A. M. and L. L. Ortman. *Condor* 55: 287, 1953.
175. Guilford, J. P. and K. M. Dallenbach. *Am. J. Psychol.* 40: 83, 1928.
176. Gunter, R. *Brit. J. Psychol.* 42: 288, 1951.
177. Haber, W. B. *J. Psychol.* 40: 115, 1955.
178. Haber, W. B. *A.M.A. Arch. Neurol. & Psychiat.* 75: 624, 1956.
179. Hardy, L. H., G. Rand and M. C. Rittler. *A.M.A. Arch. Ophth.* 45: 53, 1951.
180. Harlow, H. F. *J. Comp. Physiol.* 27: 467, 1939.
181. Harms, H. *von Graefes Arch. Ophth.* 138: 149, 1937.
182. Harrower, M. R. *Brit. J. Psychol.* 30: 48, 1939.
183. Hartline, H. K. and F. Ratliff. *J. Gen. Physiol.* 40: 357, 1957.
184. Hartridge, H. *Recent Advances in the Physiology of Vision.* London: Churchill, 1950.
185. Hazelhoff, F. F. and H. Wiersma. *Ztschr. Psychol.* 96: 171, 1924.
186. Head, H. *Studies in Neurology.* London: Hodder & Stoughton, 1920, vol. 2.
187. Hebb, D. O. *J. Genet. Psychol.* 51: 101, 1937.
188. Hebb, D. O. *The Organization of Behavior.* New York: Wiley, 1949.
189. Heider, F. and M. Simmel. *Am. J. Psychol.* 65: 263, 1952.
190. Heil, K. H. *Ztschr. vergleich. Physiol.* 23: 1, 1936.
191. Heise, G. A. and G. A. Miller. *Am. J. Psychol.* 64: 68, 1951.
192. Held, R. *Am. J. Psychol.* 68: 526, 1955.
193. Held, R. and N. Gottlieb. *Percept. Motor Skills* 8: 83, 1958.
194. Held, R. and A. V. Hein. *Percept. Motor Skills* 8: 87, 1958.
195. Held, R. and B. White. *Science* 130: 860, 1959.
196. Helson, H. *J. Opt. Soc. Am.* 33: 555, 1943.
197. Helson, H. *Psychol. Rev.* 55: 297, 1948.
198. Helson, H. and S. M. King. *J. Exper. Psychol.* 14: 202, 1931.
199. Hering, E. *Beiträge zur Physiologie. Zur Lehre vom Ortsinne der Netzhaut.* Leipzig: Engelmann, 1861–1864.
200. Hering, E. *Zur Lehre vom Lichtsinne.* Berlin, 1878.
201. Hering, E. In: *Hermanns Handb. Physiol.* 3: 343, 1879. (*Spatial Sense and Movements of the Eye*, translated by C. A. Radde. Baltimore: Am. Acad. Optom., 1942.)
202. Hering, E. *Grundzuge der Lehre vom Lichtsinn.* Berlin: Springer, 1920.
203. Hernández-Peón, R. *Acta neurol. latinoam.* 1: 256, 1955.
204. Hernández-Peón, R., H. Scherrer and M. Jouvet. *Science* 123: 331, 1956.
205. Heron, W., B. K. Doane and T. H. Scott. *Canad. J. Psychol.* 10: 13, 1956.
206. Herter, K. *Die Fischdressuren und ihre sinnesphysiologischen Grundlagen.* Berlin: Akademie, 1953.
207. Hertz, M. *Ztschr. vergleich. Physiol.* 8. 693, 1929.
208. Hertz, M. *Ztschr. vergleich. Physiol.* 11: 107, 1930.
209. Hertz, M. *Ztschr. vergleich. Physiol.* 14: 629, 1931.
210. Hertz, M. *Ztschr. vergleich. Physiol.* 21: 604, 1934.
211. Hess, E. H. *J. Comp. & Physiol. Psychol.* 43: 112, 1950.
212. Hess, E. H. *Scient. Am.* 195(1): 71, 1956.
213. Hillebrand, F. *Denkschr. Akad. Wiss. Wien, Math.-naturw. Kl. Abt. III* 72: 255, 1902.
214. Hillebrand, F. *Ztschr. Psychol.* 89: 209, 1922.
215. Hillebrand, F. *Ztschr. Psychol.* 90: 1, 1922.
216. Hirsch, J., R. H. Lindley and E. C. Tolman. *J. Comp. & Physiol. Psychol.* 48: 278, 1955.
217. Hochberg, J. E., W. Triebel and G. Seaman. *J. Exper. Psychol.* 41: 153, 1951.
218. Holmes, G. *Brit. J. Ophth.* 2: 449, 506, 1918.
219. Holt, E. B. *Psychol. Monogr.* No. 17, 1903.
220. Holway, A. H. and E. G. Boring. *Am. J. Psychol.* 54: 21, 1941.
221. Homann, H. *Ztschr. vergleich. Physiol.* 7: 201, 1928.
222. Homann, H. *Ztschr. vergleich. Physiol.* 14: 40, 1931.
223. Honigmann, H. *Proc. Roy. Soc., London. ser. B* 132: 291, 1944.
224. Hubel, D. H. *Am. J. Ophth.* 46: 110, 1959.
225. Hulin, W. S. *J. Exper. Psychol.* 10: 293, 1927.
226. Hull, C. L. *Psychol. Rev.* 46: 9, 1939.
227. Hunter, I. M. L. *Brit. J. Psychol.* 43: 113, 1952.
228. Hunter, I. M. L. *Brit. J. Psychol.* 45: 288, 1954.
229. Hunter, I. M. L. *Quart. J. Exper. Psychol.* 6: 149, 1954.
230. Hunton, V. D. *J. Genet. Psychol.* 86: 281, 1955.
231. Hurvich, L. M. and D. Jameson. *Psychol. Rev.* 64: 384, 1957.

232. Huxley, J. S. *Proc. Zool. Soc.* 30: 491, 1914.
233. Hymovitch, B. *J. Comp. & Physiol. Psychol.* 45: 313, 1952.
234. Ilse, D. *Ztschr. vergleich. Physiol.* 17: 537, 1932.
235. Ireland, F. M. *J. Exper. Psychol.* 40: 282, 1950.
236. Ittelson, W. H. and H. Cantril. *Perception: A Transactional Approach.* New York: Doubleday, 1954.
237. Jaffe, R. *Am. J. Psychol.* 67: 668, 1954.
238. Jaffe, R. *A.M.A. Arch. Neurol. & Psychiat.* 73: 57, 1955.
239. Jasper, H. H. *Psychol. Monogr.* 43: 72, 1932.
240. Jeffress, L. A. *J. Comp. & Physiol. Psychol.* 41: 35, 1948.
241. Johanssen, G. *Configurations in Event Perception.* Uppsala: Almqvist, 1950.
242. Johanssen, G. Psychology Laboratory Reports, Stockholm University, No. 12, 1955.
243. Joynson, R. B. *Quart. J. Exper. Psychol.* 1: 119, 1949.
244. Judd, C. H. *Psychol. Rev.* 9: 27, 1902.
245. Jung, R. In: *The Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 423.
246. Kalmus, H. *Brit. J. Anim. Behav.* 2: 63, 1954.
247. Kappers, C. U. A. In: *Cytology and Cellular Pathology of the Nervous System*, edited by W. Penfield. New York: Hoeber, 1932, vol. 1, p. 45.
248. Kardos, L. *Ztschr. Psychol.* Suppl. 23, 1934.
249. Katz, D. *Ztschr. Psychol.* Suppl. 7, 1911.
250. Katz, D. *Ztschr. Psychol.* Suppl. 11, 1925.
251. Katz, D. *Der Aufbau der Farbwelt* (2nd ed.). Leipzig: Barth, 1930. (*The World of Colour*, translated by R. B. MacLeod and C. W. Fox. London: Paul, 1935.)
252. Katz, D. and G. Révész. *Ztschr. angew. Psychol.* 18: 307, 1921.
253. Katz, M. S. and I. Schwartz. *J. Opt. Soc. Am.* 45: 523, 1955.
254. Kennard, M. A. and L. Ectors. *J. Neurophysiol.* 1: 45, 1938.
255. Kepler, J. *Dioptrice.* Augsburg: Franci, 1611.
256. Klein, G. S. and D. Krech. *J. Personality* 21: 118, 1952.
257. Kleist, K. *Klin. Wchnschr.* 5: 3, 1926.
258. Klimpfinger, S. *Arch. ges. Psychol.* 88: 599, 1933.
259. Klüver, H. *Behavior Mechanisms in Monkeys.* Chicago: Univ. Chicago Press, 1933 (reprinted 1957).
260. Klüver, H. *J. Psychol.* 4: 383, 1937.
261. Klüver, H. *Biol. Symp.* 7: 253, 1942.
262. Klüver, H. In: *Studies in Personality.* New York: McGraw-Hill, 1942, p. 175.
263. Knoll, F. *Abh. zool.-bot. Ges. Wien* 12: 1, 1921.
264. Knoll, F. *Abh. zool.-bot. Ges. Wien* 12(3): 379, 1926.
265. Köhler, W. *Ztschr. Psychol.* 77: 248, 1917.
266. Köhler, W. *Abh. kgl. preuss. Akad. Wiss., Physik.-math. Kl.* 2: 3, 1918.
267. Köhler, W. *Die physischen Gestalten in Ruhe und im stationären Zustand.* Erlangen: Philos. Akad., 1920.
268. Köhler, W. *Psychol. Forsch.* 3: 397, 1923.
269. Köhler, W. *Brit. J. Psychol.* 14: 262, 1924.
270. Köhler, W. *The Mentality of Apes.* London: Paul, 1927.
271. Köhler, W. *Dynamics in Psychology.* New York: Liveright, 1940.
272. Köhler, W. *Gestalt Psychology.* New York: Liveright, 1947.
273. Köhler, W. In: *Cerebral Mechanisms in Behavior*, edited by L. A. Jeffress. New York: Wiley, 1951, p. 200.
274. Köhler, W. and D. Dinnerstein. *Miscellanea Psychologica Albert Michotte.* 1947, p. 196.
275. Köhler, W. and D. A. Emery. *Am. J. Psychol.* 60: 159, 1947.
276. Köhler, W. and J. Fishback. *J. Exper. Psychol.* 40: 267, 398, 1950.
277. Köhler, W. and R. Held. *Science* 110: 414, 1949.
278. Köhler, W., R. Held and D. N. O'Connell. *Proc. Am. Philos. Soc.* 96: 290, 1952.
279. Köhler, W., W. D. Neff and J. Wegener. *J. Cell. & Comp. Physiol.* 45, Suppl. 1: 1, 1955.
280. Köhler, W. and D. N. O'Connell. *J. Cell. & Comp. Physiol.* 49, Suppl. 2: 1, 1957.
281. Köhler, W. and H. Wallach. *Proc. Am. Philos. Soc.* 88: 269, 1944.
282. Köhler, W. and J. Wegener. *J. Cell. & Comp. Physiol.* 45, Suppl. 1: 25, 1955.
283. Koffka, K. In: *Handbuch der normalen und pathologischen Physiologie*, edited by A. Bethe, G. von Bergmann, G. Embden and A. Ellinger. Berlin: Springer, 1931, vol. 12, no. 2, p. 1166.
284. Koffka, K. *Principles of Gestalt Psychology.* New York: Harcourt, 1935.
285. Kohler, I. *Sitzber. Oesterr. Akad. Wiss., phil.-hist. Kl.* 227: 1, 1951.
286. Kohler, I. *Die Pyramide* 3: Nos. 5–7, 1953.
287. Kolb, E. *Ztschr. vergleich. Physiol.* 37: 136, 1955.
288. Kornmüller, A. E. *J. Psychol. u. Neurol.* 41: 354, 1931.
289. Korte, A. *Ztschr. Pyschol.* 72: 193, 1915.
290. Krauskopf, J. *Am. J. Psychol.* 67: 278, 1954.
291. Krauskopf, J., R. A. Duryea and M. E. Bitterman. *Am. J. Psychol.* 67: 427, 1954.
292. Krauthamer, G. *Am. Psychologist* 14: 396, 1959.
293. Krech, D. and R. S. Crutchfield. *Elements of Psychology.* New York: Knopf, 1958.
294. Krieger, H. P. and M. B. Bender. *Fed. Proc.* 8: 89, 1949.
295. Krueger, E. G., P. A. Price and H.-L. Teuber. *J. Psychol.* 38: 191, 1954.
296. Külpe, O. *Grundriss der Psychologie.* Leipzig: Engelmann, 1893, pp. 30–33.
297. Lambercier, M. *Arch. de psychol.* 31: 79, 1946.
298. Land, E. H. *Scient. Am.* 200 (5): 84, 1959.
299. Langdon, J. *Quart. J. Exper. Psychol.* 3: 157, 1951.
300. Lashley, K. S. *Brain Mechanisms and Intelligence.* Chicago: Univ. Chicago Press, 1929.
301. Lashley, K. S. *J. Gen. Psychol.* 18: 123, 1938.
302. Lashley, K. S. *J. Comp. Neurol.* 70: 45, 1939.
303. Lashley, K. S. *A.M.A. Arch. Neurol. & Psychiat.* 46: 331, 1941.
304. Lashley, K. S. *Biol. Symp.* 7: 301, 1942.
305. Lashley, K. S. *J. Genet. Psychol.* 60: 197, 1942.
306. Lashley, K. S. *Genet. Psychol. Monogr.* 37: 107, 1948.
307. Lashley, K. S. In: *Cerebral Mechanisms in Behavior*, edited by L. A. Jeffress. New York: Wiley, 1951.
308. Lashley, K. S. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 529, 1952.
309. Lashley, K. S., K. L. Chow and J. Semmes. *Psychol. Rev.* 58: 123, 1951.
310. Lashley, K. S. and J. T. Russell. *J. Genet. Psychol.* 45: 136, 1934.
311. Lawrence, M. *Studies in Human Behavior: A Laboratory Manual.* Princeton: Princeton Univ. Press, 1949.
312. Leibowitz, H. *Percept. Motor Skills* 6: 65, 1956.

313. Leibowitz, H. *Naturwissenschaften* 45: 621, 1958.
314. Leibowitz, H., P. Chinetti and J. Sidowski. *Science* 123: 668, 1956.
315. Leibowitz, H., N. A. Myers and P. Chinetti. *J. Exper. Psychol.* 50: 15, 1955.
316. Leonardo da Vinci. *Paragone* (written between 1482 and 1500), edited by I. R. Richter. New York: Oxford, 1949, p. 94.
317. Levine, J. *J. Genet. Psychol.* 67: 105, 1945.
318. Levine, J. *J. Genet. Psychol.* 67: 131, 1945.
319. Levine, J. *J. Genet. Psychol.* 81: 19, 1952.
320. Lhermitte, J. *L'Image de notre corps.* Paris: Édit. Nouv. Rev. Crit., 1939.
321. Lhermitte, J. J. and J. de Ajuriaguerra. *Psychopathologie de la vision.* Paris: Masson, 1942.
322. Liang, T. and H. Piéron. *Ann. psychol.* 43–44: 1, 1942–43.
323. Liebert, R. S. and R. G. Rudel. *Child Develop.* 30: 81, 1959.
324. Lindsley, D. B. In: *The Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 513.
325. Lissmann, H. W. *Ztschr. vergleich. Physiol.* 18: 65, 1933.
326. Lit, A. *Am. J. Psychol.* 62: 159, 1949.
327. Locke, N. M. *Arch. Psychol.* 28: No. 193, 1935.
328. Loeb, J. *Arch. ges. Physiol.* 34: 67, 1884.
329. Ludvigh, E. J. *A.M.A. Arch. Ophth.* 42: 14, 1949.
330. Lüneburg, R. K. *Mathematical Analysis of Binocular Vision.* Princeton: Princeton Univ. Press, 1947.
331. Luria, A. R. *Brain* 82: 437, 1959.
332. Mach, E. *Grundlinien der Lehre von den Bewegungsempfindungen.* Leipzig: Engelmann, 1875.
333. Mach, E. *The Analysis of Sensations*, translation by S. Waterlow. Chicago: Open Court, 1914. (First ed. in German, 1886.)
334. MacKay, D. M. *Electroencephalog. & Clin. Neurophysiol.* 5: 559, 1953.
335. MacKay, D. M. *Brit. J. Psychol.* 47: 30, 1956.
336. MacKay, D. M. *Nature, London* 180: 849, 1957.
337. MacLeod, R. B. *Arch. Psychol.* No. 135, 1932.
338. Mangold, O. *Zool. Jahrb., Abt. allg. Zool. Physiol.* 62: 441, 1951.
339. Marquis, D. G. *A.M.A. Arch. Neurol. & Psychiat.* 33: 807, 1935.
340. Marshall, W. H. and S. A. Talbot. *Biol. Symp.* 7: 117, 1942.
341. McCleary, R. A. *Am. Psychologist* 14: 399, 1959.
342. McGinnies, E. *Psychol. Rev.* 56: 244, 1949.
343. Menner, E. *Zool. Jahrb., Abt. allg. Zool. Physiol.* 58: 481, 1938.
344. Mersenne, M. *Traités de la nature des sons et des mouvements de toutes sortes de corps.* 1636.
345. Metzger, W. *Psychol. Forsch.* 13: 6, 1930.
346. Metzger, W. *Psychol. Forsch.* 20: 195, 1935.
347. Michotte, A. *La Perception de la causalité.* Louvain: Publ. Univ., 1946; 2nd ed., 1954.
348. Mittelstaedt, H. *Naturwissenschaften* 36: 90, 1949.
349. Mittelstaedt, H. In: *Recent Advances in Invertebrate Physiology*, edited by B. T. Scheer. Eugene: Univ. Oregon Pub'ns., 1957, p. 51.
350. Mohrmann, K. *Ztschr. Psychol.* 193: 145, 1939.
351. Molyneux, W. *Dioptrica Nova. A Trentise of Dioptricks, in Two Parts.* London: Tooke, 1692.
352. Moray, N. *Quart. J. Exper. Psychol.* 11: 56, 1959.
353. Mountjoy, P. T. *J. Exper. Psychol.* 56: 97, 1958.
354. Müller, G. E. *Ztschr. Psychol.* 49: 109, 1916.
355. Müller-Lyer, F. C. *Arch. Physiol.* Suppl.: 263, 1889.
356. Musatti, C. L. *Arch. ital. psichol.* 9: 61, 1931.
357. Myers, R. E. *Brain* 79: 358, 1956.
358. Neet, C. C. *J. Genet. Psychol.* 43: 163, 1933.
359. Neff, W. S. *Am. J. Psychol.* 48: 1, 1936.
360. Neuhaus, W. *Arch. ges. Psychol.* 75: 315, 1930.
361. Newton, I. *Opticks.* London, 1704; 4th ed., 1730; Query 15.
362. Nielsen, J. M. *Agnosia, Apraxia, Aphasia* (2nd ed.). New York: Hoeber, 1946.
363. Nissen, H. W., K. L. Chow and J. Semmes. *Am. J. Psychol.* 64: 485, 1951.
364. Ogle, K. N. *A.M.A. Arch. Ophth.* 20: 604, 1938.
365. Ogle, K. N. *A.M.A. Arch. Ophth.* 48: 50, 1952.
366. Oldfield, R. C. and O. L. Zangwill. *Brit. J. Psychol.* 32: 267, 1942.
367. Oldfield, R. C. and O. L. Zangwill. *Brit. J. Psychol.* 33: 58, 1942.
368. Oppel, J. J. *Jahresber. phys. Ver. Frankfurt* 37: 1854–1855.
369. Oppenheim, H. *Neurol. Centralbl.* 23: 529, 1885.
370. Orbison, W. D. *Am. J. Psychol.* 52: 31, 1939.
371. Osgood, C. E. and A. W. Heyer. *Psychol. Rev.* 59: 98, 1951.
372. Osterrieth, P. A. *Arch. de psychol.* 30: 205, 1944.
373. Pache, J. *Ztschr. vergleich. Physiol.* 17: 423, 1932.
374. Pavlov, I. P. *Conditioned Reflexes*, translated by G. V. Anrep. London: Oxford, 1927.
375. Piaget, J. *La Construction du réel chez l'enfant.* Paris: Delachaux, 1937.
376. Piaget, J. *Arch. de psychol.* 35: 1, 1955.
377. Piaget, J. and B. Inhelder. *La Représentation de l'espace chez l'enfant.* Paris: Presses univ. France, 1948.
378. Pick, A. In: *Arbeiten aus der deutschen psychiatrischen Klinik, Prag.* Berlin: Karger, 1908.
379. Pick, A. *Psychol. Forsch.* 1: 303, 1921.
380. Piéron, H. *Ann. Psychol.* 23: 186, 1922.
381. Pitts, W. and W. S. McCulloch. *Bull. Math. Biophys.* 9: 127, 1947.
382. Plateau, J. A. F. *Correspondance math. phys. Observatoire Bruxelles* 7: 365, 1832.
383. Plateau, J. A. F. *Bull. acad. sci. Belg.* 16 (2): 254, 1850.
384. Plateau, J. A. F. *Bull. acad. sci. Belg.* 33 (2e sér.): 376, 1872.
385. Ponzo, M. *Arch. ges. Psychol.* 65: 129, 1928.
386. Poppelreuter, W. *Die psychischen Schadigungen durch Kopfschuss im Kriege 1914–16: Die Störungen der niederen und höheren Schleistungen durch Verletzung des Okzipitalhirns.* Leipzig: Voss, 1917.
387. Porta, J. B. *Magiae naturalis.* Naples, 1558; 2nd ed. 1591; English translation, *Natural Magick.* London: Young and Speed, 1658.
388. Prentice, W. C. H. and D. C. Beardslee. *J. Exper. Psychol.* 40: 355, 1950.
389. Pritchard, R. M. *Quart. J. Exper. Psychol.* 10: 77, 1958.
390. Pulfrich, C. *Naturwissenschaften* 10: 533, 569, 714, 735, 751, 1922.
391. Purdy, D. M. *Am. J. Psychol.* 49: 313, 1937.
392. Purkinje, J. B. *Med. Jahrb. oesterr. Staates* 6: 79, 1820.
393. Purkinje, J. B. *Beobachtungen und Versuche zur Physiologie*

*der Sinne. II. Neue Beiträge zur Kenntnis des Scheas in subjektiver Hinsicht.* Berlin, 1825.
394. Ratliff, F. and L. A. Riggs. *J. Exper. Psychol.* 40: 687, 1950.
395. Ratoosh, P. *Proc. Nat. Acad. Sc., Washington* 35: 257, 1949.
396. Rayleigh, Lord (J. W. Strutt). *Proc. Mus. A.*, p. 75, 1875–1876.
397. Révész, G. *VII Internat. Congr. Psychol., Proc.* 29, 1924.
398. Révész, G. *Ztschr. Psychol.* 131: 296, 1934.
399. Riddoch, G. *Brain* 49: 15, 1917.
400. Riesen, A. H. *Science* 106: 107, 1947.
401. Riesen, A. H. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 425.
402. Riesen, A. H. and L. Aarons. *J. Comp. & Physiol. Psychol.* 52: 142, 1959.
403. Riesen, A. H., M. I. Kurke and J. C. Mellinger. *J. Comp. & Physiol. Psychol.* 46: 166, 1953.
404. Riggs, L. A., F. Ratliff, J. C. Cornsweet and T. N. Cornsweet. *J. Opt. Soc. Am.* 43: 495, 1953.
405. Rosenzweig, M. R. *J. Comp. & Physiol. Psychol.* 47: 269, 1954.
406. Rubin, E. *Synsoplevede Figurer*. Copenhagen: Gyldendalska, 1915. (German ed., *Visuell Wahrgenommene Figuren*. Copenhagen: Gyldendalska, 1921.)
407. Rudel, R. G. *J. Comp. & Physiol. Psychol.* 50: 292, 1957.
408. Rudel, R. G. *J. Comp. & Physiol. Psychol.* 51: 386, 1958.
409. Rüssel, A. *Neue psychol. Stud.* 7: 1, 1931.
410. Sagara, M. and T. Oyama. *Psychol. Bull.* 54: 327, 1957.
411. Sandström, C. I. *Orientation in the Present Space*. Uppsala: Almqvist, 1951.
412. Sauer, F. *Ztschr. Tierpsychol.* 14: 29, 1957.
413. Schlosberg, H. *Am. J. Psychol.* 54: 601, 1941.
414. Scholz, W. *Psychol. Forsch.* 5: 219, 1924.
415. Schumann, F. *Ztschr. Psychol.* 23: 1, 1900.
416. Schur, E. *Psychol. Forsch.* 7: 44, 1925.
417. Semmes, J. *Psychol. Rev.* 60: 140, 1953.
418. Semmes, J., S. Weinstein, L. Ghent and H.-L. Teuber. *J. Psychol.* 39: 227, 1955.
419. Semon, R. *Die Mneme* (3rd ed.). Leipzig, 1911.
420. Settlage, P. H. *J. Comp. Psychol.* 27: 93, 1939.
421. Settlage, P. H. *J. Comp. Psychol.* 27: 109, 1939.
422. Shannon, C. E. *Bell System Tech. J.* 30: 50, 1951.
423. Shapiro, M. B. *Brit. J. Psychol.* 45: 58, 1954.
424. Sharpless, S. and H. H. Jasper. *Brain* 79: 655, 1956.
425. Sherif, M. *Arch. Psychol.* No. 187, 1935.
426. Sherrington, C. S. *The Integrative Action of the Nervous System*. New Haven: Yale Univ. Press, 1906; reprinted London: Cambridge, 1947, p. 353.
427. Shipley, T. *J. Opt. Soc. Am.* 47: 795, 1957.
428. Shipley, T. *J. Opt. Soc. Am.* 47: 804, 1957.
429. Siegel, A. I. *J. Comp. & Physiol. Psychol.* 46: 115, 1953.
430. Siegel, A. I. *J. Comp. & Physiol. Psychol.* 46: 249, 1953.
431. Snyder, F. W. and N. H. Pronko. *Vision with Spatial Inversion*. Wichita: Univ. Kansas Press, 1952.
432. Sokolov, N. *Perception and the Conditioned Reflex*. Moscow: Moscow Univ. Press, 1958.
433. Spemann, H. *Embryonic Development and Induction*. New Haven: Yale Univ. Press, 1938.
434. Spencl, K. W. *Psychol. Rev.* 44: 430, 1937.
435. Spence, K. W. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951, p. 690.
436. Sperry, R. W. *J. Exper. Zool.* 92: 263, 1943.
437. Sperry, R. W. *Quart. Rev. Biol.* 20: 311, 1945.
438. Sperry, R. W. *J. Comp. & Physiol. Psychol.* 43: 482, 1950.
439. Sperry, R. W. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 401.
440. Sperry, R. W. and E. Clark. *Physiol. Zool.* 22: 372, 1949.
441. Sperry, R. W. and N. Miner. *J. Comp. & Physiol. Psychol.* 48: 463, 1955.
442. Sperry, R. W., N. Miner and R. E. Myers. *J. Comp. & Physiol. Psychol.* 48: 50, 1955.
443. Spitz, H. H. *Psychol. Bull.* 55: 1, 1958.
444. Stein, H. *Deutsche Ztschr. Nervenh.* 80: 218, 1923.
445. Stein, H. and V. von Weizsäcker. *Deutsches Arch. klin. Med.* 151: 230, 1926.
446. Stern, A. *Psychol. Forsch.* 7: 1, 1926.
447. Stern, W. *Ztschr. angew. Psychol.* 2: 498, 1909.
448. Stern, W. *Psychology of Early Childhood* (2nd ed.). London: Allen, 1930.
449. Stevens, S. S. *Proc. Nat. Acad. Sc., Washington* 20: 457, 1934.
450. Stevens, S. S. *J. Acoust. Soc. Am.* 8: 191, 1937.
451. Stevens, S. S. *Science* 127: 383, 1958.
452. Stevens, S. S. *Am J. Psychol.* 71: 633, 1958.
453. Stevens, S. S. and E. H. Galanter. *J. Exper. Psychol.* 54: 377, 1957.
454. Stigler, R. In: *Handbuch der biologischen Arbeitsmethoden*, edited by E. Abderhalden. Berlin: Urban, 1926, sect. v, pt. 6, 2nd half.
455. Stratton, G. M. *Psychol. Rev.* 3: 611, 1896.
456. Stratton, G. M. *Psychol. Rev.* 4: 182, 1897.
457. Stratton, G. M. *Psychol. Rev.* 4: 341, 463, 1897.
458. Sumner, F. B. *Proc. Nat. Acad. Sc., Washington* 10: 559, 1934.
459. Sutherland, N. S. *Nature, London* 179: 11, 1957.
460. Sutherland, N. S. *Brit. J. Psychol.* 48: 55, 1957.
461. Sutherland, N. S. *Quart. J. Exper. Psychol.* 10: 40, 1958.
462. Tausch, R. *Psychol. Forsch.* 24: 299, 1954.
463. Taylor, J. G. and S. Papert. *Brit. J. Psychol.* 47: 216, 1956.
464. Teas, D. C. and M. E. Bitterman. *Psychol. Rev.* 59: 130, 1952.
465. Teuber, H.-L. In: *Recent Advances in Psychologic Testing*, edited by R. Harris. Springfield: Thomas, 1950, p. 30.
466. Teuber, H.-L. *Ann. Rev. Psychol.* 6: 267, 1955.
467. Teuber, H.-L. In: *Evolution of Nervous Control*. Washington, D. C.: Am. A. Adv. Sc., 1959, p. 157.
468. Teuber, H.-L., W. S. Battersby and M. B. Bender. *Am. J. Physiol.* 159: 592, 1949.
469. Teuber, H.-L., W. S. Battersby and M. B. Bender. *Visual Field Defects After Penetrating Missile Wounds of the Brain*. Cambridge: Harvard Univ. Press, 1960.
470. Teuber, H.-L. and M. B. Bender. *Tr. Am. Neurol. A.* 174, 1948.
471. Teuber, H.-L. and M. B. Bender. *Fed. Proc.* 7: 123, 1948.
472. Teuber, H.-L. and M. B. Bender. *Am. Psychologist* 3: 246, 1948.
473. Teuber, H.-L. and M. B. Bender. *J. Gen. Psychol.* 40: 37, 1949.
474. Teuber, H.-L. and M. B. Bender. *Am. Psychologist* 5: 271, 1950.

475. Teuber, H.-L., H. P. Krieger and M. B. Bender. *Fed. Proc.* 8: 156, 1949.
476. Teuber, H.-L. and R. S. Liebert. *Am. Psychologist* 11: 430, 1956.
477. Teuber, H.-L. and R. S. Liebert. *A.M.A. Arch. Neurol. & Psychiat.* 80: 403, 1958.
478. Teuber, H.-L. and M. Mishkin. *J. Psychol.* 38: 161, 1954.
479. Teuber, H.-L. and S. Weinstein. *A.M.A. Arch. Neurol. & Psychiat.* 76: 369, 1956.
480. Thayer, G. H. and A. H. Thayer. *Concealing Coloration in the Animal Kingdom.* New York: Macmillan, 1909.
481. Thomas, G. J. *Am. J. Psychol.* 68: 37, 1955.
482. Thomas, G. J. and P. A. Stewart. *Am. J. Psychol.* 70: 528, 1957.
483. Thompson, W. R. and W. Heron. *Canad. J. Psychol.* 8: 17, 1954.
484. Thouless, R. H. *Brit. J. Psychol.* 21: 339, 1931.
485. Thouless, R. H. *Brit. J. Psychol.* 22: 1, 1931.
486. Tinbergen, N. *The Study of Instinct.* New York: Oxford, 1951.
487. Tinbergen, N. *J. Comp. & Physiol. Psychol.* 50: 412, 1957.
488. Towe, R. L. *J. Comp. & Physiol. Psychol.* 47: 283, 1954.
489. Vernon, M. D. *Visual Perception.* London: Cambridge, 1937.
490. Vernon, M. D. *A Further Study of Visual Perception.* London: Cambridge, 1952.
491. Visser, J. A. and G. G. J. Rademaker. *Arch. néerl. Physiol.* 20: 103, 284, 1935.
492. Visser, J. A. and G. G. J. Rademaker. *Arch. néerl. Physiol.* 22: 398, 1937.
493. Volkelt, H. *Ber. IV Kongr. Heilpäd.*, Leipzig, 1928; Berlin, 1929.
494. von Allesch, J. *Zur nichteuklidischen Struktur des phänomenalen Raumes. (Versuche an Lemur mongoz mongoz L.).* Jena: Fischer, 1931.
495. von Buddenbrock, W. *Vergleichende Physiologie. I. Sinnesphysiologie.* Basel: Birkhäuser, 1952.
496. von Ehrenfels, C. *Vjschr. wiss. Philos.* 14: 249, 1890.
497. von Fieandt, K. *Über das Sehen von Tiefengebilden bei wechselnder Beleuchtungsrichtung.* Helsinki: Psychol. Inst., Univ. Helsinki, 1938.
498. von Frey, M. *Ztschr. Biol.* 56: 574, 1911.
499. von Frisch, K. *Zool. Jahrb., Abt. allg. Zool. Physiol.* 35: 1, 1914.
500. von Frisch, K. *Bees, Their Vision, Chemical Senses, and Language.* Ithaca: Cornell Univ. Press, 1950.
501. von Helmholtz, H. *Handbuch der physiologischen Optik.* Leipzig: Voss, 1856, 1860, 1866, 3 vols.
502. von Helmholtz, H. *Physiological Optics*, translated and edited by J. P. Southall. New York: Optical Soc. Am., 1925, 3 vols.
503. von Holst, E. *Symp. Soc. Exper. Biol.* 4: 143, 1950.
504. von Holst, E. *Studium Generale* 10: 231, 1957.
505. von Holst, E. and H. Mittelstaedt. *Naturwissenschaften* 37: 464, 1950.
506. von Hornbostel, E. M. In: *Handbuch der normalen und pathologischen Physiologie*, edited by A. Bethe, G. von Bergmann, G. Embden and A. Ellinger. Berlin: Springer, 1930, vol. 11, p. 602.
507. von Hornbostel, E. M. and M. Wertheimer. *Sitzber. kgl. preuss. Akad. Wiss.* 388, 1920.
508. von Schiller, P. *Psychol. Forsch.* 17: 179, 1933.
509. von Schiller, P. *Ztschr. vergleich. Physiol.* 20: 454, 1934.
510. von Schiller, P. *J. Comp. & Physiol. Psychol.* 44: 101, 1951.
511. von Senden, M. *Raum- und Gestaltauffassung bei operierten Blindgeborenen vor und nach der Operation.* Leipzig: Barth, 1932.
512. von Tschermak-Seysenegg, A. *Arch. ges. Physiol.* 241: 454, 1939.
513. von Tschermak-Seysenegg, A. *Docum. ophth.* 2: 10, 1948.
514. Wald, G. and H. M. Burian. *Am. J. Ophth.* 27: 950, 1944.
515. Walk, R. D., E. J. Gibson and T. J. Tighe. *Science* 126: 80, 1957.
516. Wallach, H. *Psychol. Rev.* 46: 541, 1939.
517. Wallach, H. *J. Exper. Psychol.* 27: 339, 1940.
518. Wallach, H. *J. Exper. Psychol.* 38: 310, 1948.
519. Wallach, H. and D. N. O'Connell. *J. Exper. Psychol.* 45: 205, 1953.
520. Wallach, H., D. N. O'Connell and U. Neisser. *J. Exper. Psychol.* 45: 360, 1953.
521. Walls, G. L. *Am. J. Optom.* Monogr. 117, 1951.
522. Wapner, S. and H. Werner. *Perceptual Development: An Investigation within the Framework of Sensory Tonic Field Theory.* Worcester: Clark Univ. Press, 1957.
523. Weber, E. H. *De Pulsu, Resorptione, Auditu et Tactu*, 1834, pp. 86–92, 132–142, 159–161.
524. Weill, G. and C. Pfersdorff. *Ann. méd.-psychol.* 93: 367, 1935.
525. Weinstein, S. *J. Comp. & Physiol. Psychol.* 48: 203, 1955.
526. Weinstein, S., J. Semmes, L. Ghent and H.-L. Teuber. *J. Psychol.* 42: 249, 1956.
527. Weinstein, S., J. Semmes, L. Ghent and H.-L. Teuber. *J. Comp. & Physiol. Psychol.* 51: 269, 1958.
528. Weinstein, S. and H.-L. Teuber. *Science* 125: 1036, 1957.
529. Weiskrantz, L. *Nature, London* 181: 1047, 1958.
530. Weiss, P. *Comp. Psychol. Monogr.* 17, No. 4 (whole No. 88), 1941.
531. Weiss, P. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 3, 1952.
532. Welch, K. and P. Stuteville. *Brain* 81: 341, 1958.
533. Wells, M. J. and J. Wells. *Pubbl. staz. zool. Napoli* 28 94, 1956.
534. Werner, H. *Am. J. Psychol.* 47: 40, 1935.
535. Werner, H. and S. Wapner. *J. Exper. Psychol.* 43: 68, 1952.
536. Wertheimer, M. *Ztschr. Psychol.* 61: 161, 1912.
537. Wertheimer, M. *Psychol. Forsch.* 4: 301, 1923.
538. Wertheimer, Michael. *Am. J. Psychol.* 64: 133, 1951.
539. Wertheimer, Michael and E. Aronson. *J. Gen. Psychol.* 58: 41, 1958.
540. Wheatstone, C. *Tr. Roy. Soc., London* 371, 1838.
541. Wilbrand, H. *Ztschr. Augenheilk.* 58: 197, 1925–26.
542. Witkin, H. A. *J. Personality* 19: 1, 1950.
543. Witkin, H. A. *J. Exper. Psychol.* 40: 93, 1950.
544. Witkin, H. A. and associates. *Personality Through Perception.* New York: Harper, 1954.
545. Wohlgemuth, A. *Brit. J. Psychol. Monogr.* Suppl. 1: 1, 1911.
546. Wolf, E. *Ztschr. vergleich. Physiol.* 20: 151, 1933.
547. Wolpert, I. *Ztschr. ges. Neurol. Psychiat.* 93: 397, 1924.
548. Woodworth, R. S. *Psychol. Bull.* 3: 68, 1906.
549. Woodworth, R. S. and H. Schlosberg. *Experimental Psychology* (revised ed.). New York: Holt, 1954.
550. Wundt, W. *Beiträge zur Theorie der Sinneswahrnehmung.* Leipzig: Winter, 1862, p. 158.

551. WUNDT, W. *Grundzüge der physiologischen Psychologie* (1st ed.). Leipzig: Engelmann, 1874; up to 6th ed., 1908–1911.
552. WUNDT, W. *Phil. Stud.* 14: 1, 1898.
553. YAMANE, K. *Jap. J. Psychol.* 10: 327, 1935.
554. YOUNG, R. T. *J. Exper. Zool.* 20: 457, 1916.
555. ZEIGLER, H. P. AND H. LEIBOWITZ. *Am. J. Psychol.* 70: 106, 1957.
556. ZEIGLER, H. P. AND H. LEIBOWITZ. *J. Comp. & Physiol. Psychol.* 51: 155, 1958.
557. ZERRAHN, G. *Ztschr. vergleich. Physiol.* 20: 117, 1933.
558. ZETTERSTROM, B. *Acta physiol. scandinav.* 35: 272, 1956.
559. ZÖLLNER, F. *Ann. Physik. Chem.* 186: 500, 1860.
560. ZUCKERMAN, C. B. AND I. ROCK. *Psychol. Bull.* 54: 269, 1957.
561. ZURMÜHL, G. *Ztschr. Sinnesphysiol.* 61: 40, 1930.

CHAPTER LXVI

# Thinking, imagery and memory

WARD C. HALSTEAD *University of Chicago, Chicago, Illinois*

CHAPTER CONTENTS



THE STUDENT OF NEUROPHYSIOLOGY will sense in this chapter that he is plunging directly into the 'thick of thin things.' Yet he can, upon reflection, concede that every word, sentence and idea of this volume represents an interplay of thinking, imagery and memory. If importance be assigned to its contents, then the relevance of an attempt to understand these aspects of the brain becomes clear. It is, of course, impossible to give more than a selected contemporaneous view of our subject. Excellent historical and supplementary discussions may be found in Fearing, *Reflex Action* (10); Boring, *History of Experimental Psychology* (4); and Herrick, *The Evolution of Human Nature* (20).

## THINKING DEFINED

Thinking is a form of problem-solving behavior which involves the correlation and integration of critical events in time and space. It is characterized by *a)* a period of preliminary exploration, *b)* a presolution period of search, *c)* a period of vicarious testing of tentative solution, *d)* an act of closure and registry of a memory trace, and *e)* appropriate action. The essential process of thinking is the bringing together or grouping of critical events in time and space. If we analyze the key terms in this proposition, it is apparent that the term 'critical events,' so far as the brain is involved, is synonymous with information, with the technical restraints of information theory (44). The terms 'time' and 'space' are synonymous with the generic parameters of the physical universe. Before we analyze the neuropsychological mechanisms which underlie these key terms, let us look once more at the general attributes of thinking.

## THINKING AS CORRELATION AND INTEGRATION

Biological science is quite familiar with the term 'integration' and perhaps to a lesser extent with the term 'correlation.' It shall be our immediate purpose to indicate that the term 'thinking' is an envelope term to cover the biological operations of correlation and integration. The importance of this analysis arises from the fact that in recent years considerable scientific progress has been made in our attempt to understand the mechanisms of integration and correlation in the central nervous system. We shall in the following avoid where possible the private subjectivism commonly implied in the layman's use of the term 'thinking' and restrict its use here to imply correlation and integration. This is not to deny the role of conscious experience in many forms of problem-solving behavior; but since consciousness may have its own neurology and physiology, it will help our understanding to set it aside momentarily for separate consideration.

*Neural and Humoral Forms of Information*

The mind stuff or information which requires to be correlated and integrated by the brain consists of *a*) specific sensory input from the classical receptors, *b*) specific and nonspecific afferent feedbacks, *c*) specific and nonspecific efferent outflows, *d*) specific and nonspecific memory traces, and *e*) 'noise.' These are the ingredients of organized behavior whether the prevailing set of the system be predominantly for perception, learning, emotion or thinking. It is not feasible to elaborate upon each of them here, but we shall return to a consideration of their formal properties as we attempt to relate them to the warp and woof of neural structure. It is reasonable to suppose that neurochemistry is intimately involved in each of the above mechanisms, but the critical correlations and integrations in this area must await future developments (28).

*Nature of Explanation*

When does thinking begin and when can it be said to reach an ending? In other words, is thinking comprised of a train of events characterized by a distinct 'on' and a distinct 'off' effect? In general, the answer to both parts of this question is yes. Thinking begins with the conscious awareness of a problem. It terminates for the particular problem by the emergence of a satisfactory solution or explanation. Whitehead has defined an explanation as "that stage where curiosity ceases." While reduction or cessation of curiosity is symptomatically related to the end-stage of thinking for the individual, it is doubtful that this is a reliable index. It may be necessary without being sufficient.

*Canonical Form of Explanation*

The 'off' effect for thinking occurs when the canonical form of classification of the critical events of the particular problem is achieved. The canonical form of thought is the paradigm of all organized knowledge. It is characterized by *a*) reduction or cessation of specific curiosity, and *b*) maximal security as to adequacy of solution or explanation. A problem may be said to be solved when its critical events can be ordered as to homology, analogy and an emergent. These are the cardinal categories of science. They serve equally the individual and the group for testing the creative or emergent against the background of organized knowledge.

MODEL FOR THINKING ABOUT THINKING

At the outset of our discussion a five-stage model of thinking behavior was set forth. In adopting it the writer has been influenced by his colleagues, by other investigators and by thoughtful and stimulating discussions of these matters with several students who have participated over the years in his graduate seminar on higher brain functions.

*Stages of Thinking Behavior*

PERIOD OF PRELIMINARY EXPLORATION. As may be seen in figure 1, thinking begins with a presenting stimulus situation which is coercive (curiosity arousing, attention demanding) for exploration. It begins as specific sensory input from one or more of the classical receptors (eye, ear, etc.). This input is organized *ab initio* into figure-ground relationship (Koehler, Lashley) or 'primitive unity' (Hebb). The primitive unity of a figure is segregated from the ground which, in turn, depends on the prevailing pattern of excitation and the inherited characteristics of the nervous system. The unity is relatively independent of past experience. The figure-ground configuration is scanned rapidly (the A Factor of Halstead) for homologous or analogous match with specific memory traces of past experience. If a prompt

FIG. 1. A figure-ground configuration illustrating the sequence of prototype questions arising in perception and thinking, "What is this?"; "What could it be?"; "What must it be?"

match (requiring milliseconds) is forthcoming, recognition or perceptual identification is said to have occurred. Low-level resolution of the task has resulted short of thinking.

At the very beginning of the first stage, the available array of organized avenues of input and output (the Modality or directional Factor D of Halstead) is scanned for pertinence. The prototype question here is, "How should I look at (conceive of) this problem?"; "What organized response is required?"

PRESOLUTION PERIOD OF SEARCH. When in the face of an 'emergent' or new situation resolution has not been successful at the first stage, the individual is delayed in adaptive response until more information is available to the neural pool through further exploration. At this point 'milking' of the stimulus for its parameters (the relata and relations of Klüver) proceeds. The prototype question "What is this?" changes to "What could this be?" Here nonspecific memory traces are scanned (the M Factor of Halstead) and tested for pertinence. Appropriate degrees of 'arousal' or power (the P Factor of Halstead) improve the signal-to-noise ratio of the task or 'nonsensory image' (Hebb) carried neurally at this stage, primarily by nonspecific afferent loops and afferent feedbacks. As in the first stage the quest for appropriate D Factor is sustained. Depending upon the complexity of the task, the information available and the stress demands for action, the need for higher 'arousal' or P Factor to protect the task from the ambient noise of individual ground fluctuations increases.

PERIOD OF VICARIOUS TESTING OF TENTATIVE SOLUTION. In the face of mounting tension or frustration, held in regulation by appropriate levels of P Factor, the individual begins to make abortive or vicarious attempts at response (the vicarious trial-and-errors, V.T.E., of Tolman). Here the prototype question is, "What happens if I handle the problem this way?" At this point specific and nonspecific memory traces are scanned and melded with abortive afferent feedbacks (proprioception). The 'as if' (Vahinger) of incipient action feeds preliminary data into the neural pool. At this stage of the task the individual exhibits mimetic signs of impending consummatory response, notably the autonomic changes described by Kellogg *et al.* (29), Lacey & Smith (36) and Malmo *et al.* (41, 42), and the electromyographic changes observed by Max (43) and Jacobson (25).

ACT OF CLOSURE AND REGISTRY OF A MEMORY TRACE. In the preceding stages the task has been held 'open' to the repetitive mechanisms of scanning, permitting reattending to the sensory input or to relevant memory traces, raising the affective loadings of some, lowering that of others. This latter landscaping or 'equalizing' of the pertinent elements of the task appears to precede slightly the act of closure and the registry of an enduring memory trace. It is perhaps this fact that makes the content of organized categories equiavailable to recall as opposed to the differential availability of unorganized elements according to Halstead (14). It may also be economical to the organism in that the events of the third stage, involving vicarious trial-and-error testing of tentative solutions, are protected from premature registry of enduring fragmented memory traces. The enduring trace is somehow held in abeyance until solution is reached.

The act of closure involves the final stage in the phenomenal selection and organization of the information in the neural pool. Essential similarities have been grouped into prevailing figure; nonessential elements and detail have been rejected from the figure. Then suddenly, 'as in a flash' (as emphasized by Poincairé and Wertheimer), closure or insight occurs. All of the necessary and sufficient elements of the task fall into place, including the appropriate modality or response system for exteriorization, the 'final common pathway' of Sherrington. A solution has been reached; the answer has been found. Less than one per cent of the general population perceives in milliseconds the visual information of figure 1 as a cow. Yet it is actually a very grainy, face-on photograph of a white-faced cow (black ears, black muzzle, white body). With this important 'modality clue,' the reader may wish to re-explore the information of figure 1. He may 'see' many fragmentary forms or details before the organization of the picture as a whole becomes compelling. Once this occurs, however, the associated memory trace will be enduring indefinitely (15).

APPROPRIATE ACTION. In general, closely related in time to the events of the fourth stage is the adoption of a 'correct' response or mode of action appropriate to the task. This consummatory response or action proceeds with great certainty (low anxiety) as to the outcome. The emotional tension induced by the sustained task is relieved. The thinking job is finished. The board (neural pool) is somehow cleared for new tasks.

The time dimension for thinking behavior is extremely elastic. While the evidence is essentially introspective in character, creative thinkers in the arts,

literature and science tend to agree that periods of reflection, tranquility and even of solitude may favor the emergence of significant ideas.

*The Necessary and Sufficient*

In the above paradigm of thinking behavior we have attempted to reduce the manifest complexity to its essentials. Is something still lacking? Do the neural mechanisms provided for in our model offer sufficient degrees of freedom for the great range of adaptive behavior characteristic of *Homo sapiens*? In thinking about the model the writer turns to the analogy of a television receiver. Obviously one could specify the rather complex circuitry of such a machine, detect operationally that it is turned on or 'aroused,' check electronically that information is coursing through all parts of the primary circuits, and still not have a picture on the screen. A 'focusing circuit' could be defective or absent.

Do we need to postulate something analogous to a focusing circuit as the 'little man' who directs attention or conscious awareness first this way, then that? There is experimental evidence which suggests that we do. Klüver (31), for example, studied eidetic imagery in children and adults. Such imagery is characterized by almost photographic fidelity in the degree of detail which is present in the recalled memory trace. Shown a black and white picture of numerous objects, the eideticer can, following brief delay, project onto a gray background a remarkably detailed copy of the picture any parts of which can be enhanced in vividness 'at will' with blurring of the remainder.

There is as yet no clue as to the special neurophysiology of differential attention (focusing). It is possible that the heightened consciousness of patterns of excitation thus implied is the epiphenomenal accompaniment of differential attention. The possible involvement of the amygdala complex in attention has been suggested by Lesse (39) and Gloor (Chapter LVIII of this *Handbook*).

Conversely, it may be that the neural elements which mediate the highest levels of correlation and integration are characterized by relatively high excitatory thresholds. Thus the closure effect may require the patterned summation of relatively large segments of the neural pool to bring off high levels of consciousness or attention (8, 16, 55).

*Methods of Studying Thinking*

The introspective method for the study of thinking has been widely employed in the past. However, the dependency of this method upon the language process, which is slow, cumbersome and quite loosely coupled to the internal processes of thinking, has limited the fruitfulness of this approach. To a considerable extent these limitations are shared by the projective techniques as applied to thinking behavior.

In addition to the well-known problem-solving studies of Maier (40), experimental studies of thinking behavior in man have been carried out by Hull (24), Smoke (52), Heidbreder (19), Halstead (14, 15), Goldstein (13), Hanfmann & Kasanin (17), and others. The general technique here has involved the presentation of a series of stimulus objects with one or more properties in common but differing in many others. The task of the subject is to derive and generalize the basis of essential similarity in the presence of dissimilarities, and vice versa.

The electroencephalogram (EEG) has thus far proved of little use as a tool for studying the thinking process (1, 18). There are, however, developments under way in this area which may have considerable significance. Brazier & Casby (5, 6) and Barlow & Brazier (2) have applied correlation techniques directly to EEG recording. Autocorrelations and cross-correlations have been obtained from homologous and nonhomologous brain areas of normal subjects, from

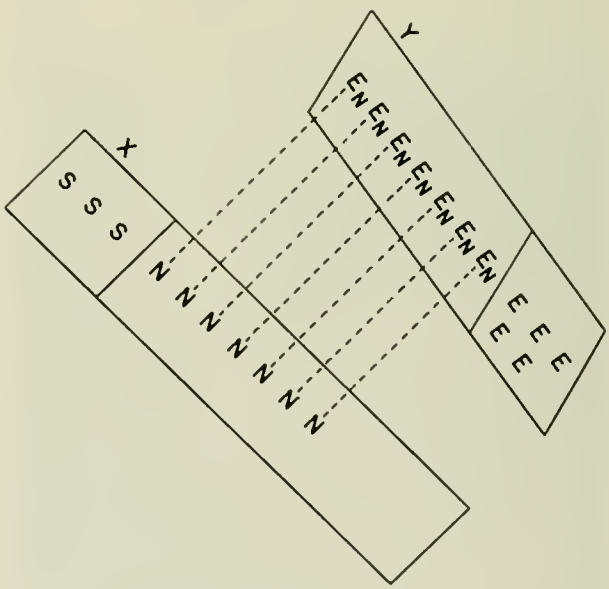



FIG. 2. Hypothetical correlation between nonspecific efferent outflows to the periphery ($Y$) and nonspecific afferent (proprioceptive) feedbacks to the neural pool ($X$) with facilitating effect on thinking behavior. (See discussion of the second and third stages of thinking behavior in text.) $S$, specific elements, $N$, nonspecific elements; $E$, efferent outflows; and $E_N$, efferent outflows phenomenally coupled to $N$.

subjects with brain lesions, from normal subjects under influence of certain drugs and from lower animals. Correlation technique, as applied to EEG data, permits systematic variation of the time dimension in an ongoing train of space-time events.

The coefficient of correlation is a convenient mathematical expression of coincidence in time and space. Multiple correlation techniques permit similar handling of multiple variable problems (see fig. 2).

If it were possible to place electrodes, strain gauges, flow meters, thermistors and chemoindicators in such way throughout the brain as to isolate and identify critical variables in the neural pool, the resulting correlation matrix generated by comparing each variable against every other variable would remain beyond comprehension, without some means of integration.

It is possible that a method known as factor analysis will supply such integration. A model illustrating the significance of this method appears in figure 3. Factor analysis has already been applied successfully as a secondary check on experimentally isolated functions in neurosurgical cases (15). It would be interesting to know, for example, whether factor analysis of anatomicophysiologic data would confirm the existence and boundaries of such a priori neural systems as the reticular, limbic, rhinencephalic and centrencephalic.

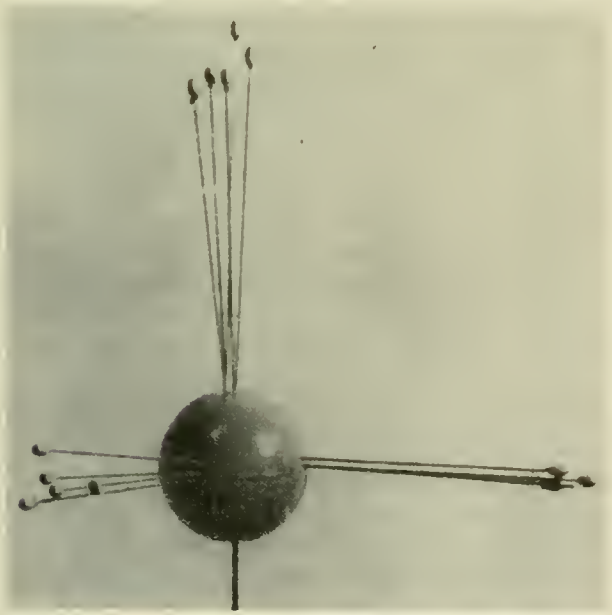


FIG. 3. Spherical model projection of factor analysis solution of 15-variable problem reduced to 3 factors. Each spindle or vector represents an individual test. For each cluster of tests a 'factor' is postulated. [From Thurstone (56).]

BIOLOGICAL INTELLIGENCE

From the study of behavioral effects of selective ablation of various parts of the brain in man, and appropriate controls, Halstead (15) has developed a concept of biological intelligence. This form of intelligence is relatively independent of that presumably reflected in the standardized psychometric test of intelligence which yields an intelligence quotient (I.Q.). Whereas the I.Q. appears to predict reasonably well the ability of the individual to perform secondary school work and less well college work, it does not predict reliably the deficits in general adaptive capacity which tend to be characteristic of forebrain (frontal lobe) lesions in man. Biological intelligence matures somewhere around 14 to 15 years of age and may, in some individuals, be maintained at a high level even through the sixth and seventh decades of life. It appears to its author to have maximal representation in the cortex of the frontal lobes since neurosurgical lesions in this area produce the greatest deficits. It is, however, directly represented to a lesser degree throughout the cerebral cortex and quite possibly in some subcortical structures. Halstead regards the frontal lobes as representing the last stage in the evolution of cortical mechanisms and holds that analysis of their functions provides an important clue to cortical mechanisms in general.

Other investigators, including Reitan (50), using

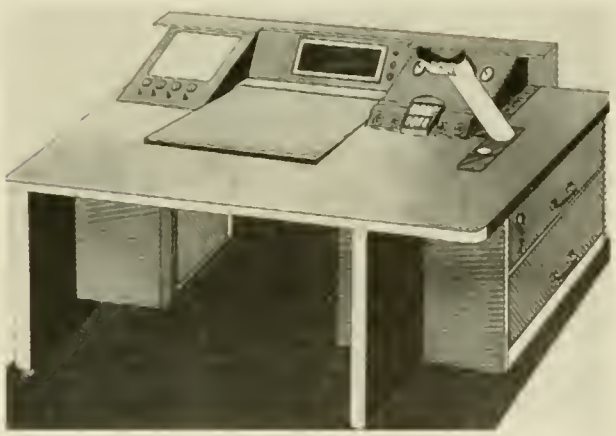


FIG. 4. Apparatus developed at the University of Chicago for measuring higher brain functions in man. The apparatus provides stimulus material of various levels of complexity for the eye, the ear and the sense of touch. All responses are objective and nonverbal in character. The data are programed on IBM cards. See text, and Halstead (15) and Reitan (50) for discussion of the various indicators employed in the apparatus.

the standardized methodology developed by Halstead over the past 20 years at the University of Chicago, are in agreement that his index provides a reliable and sensitive indicator of brain lesions in man. There is still substantial disagreement as to whether the principle of mass action (Lashley) applies throughout the cerebral cortex in relation to biological intelligence. Halstead has organized the 10 separate indicators which comprise his measures of biological intelligence into the testing console shown in figure 4. With the help of a trained technician working in a suitable environment, the testing apparatus makes possible the presentation of approximately 5,000 controlled stimuli through the modalities of vision, hearing and sense of touch. The stimuli are programed in such manner that the level of organization (starting from simple discriminations to complex organization) of stimuli can be specified from the objective responses of the individual subject. All interpretations are done by a third party without sensory contact with the subject or without prior knowledge of the medical history. The components of the Halstead Battery of Tests consists of a category test (with instantaneous auditory reinforcement of correct and incorrect responses); a tactual form-board test (which is never experienced visually by the subject); a test for critical fusion frequency; a test for auditory flutter-fusion frequency (frequency of interruption at which bursts of white noise fuse subjectively into continuous noise); a speech perception test; a rate of tapping test; and a time-sense memory test (repeated setting of an electric clock with and without the aid of vision). In developing these indicators as measures of biological intelligence, Halstead has studied their performance in *a*) hundreds of neurosurgical cases; *b*) several hundred normal controls including subgroups matched for age, sex, I.Q., amount of formal education, occupational level and ethnic origin; *c*) normal young men temporarily under the stress of low-oxygen environment or simulated high altitude; *d*) psychiatric patients falling in various diagnostic categories including schizophrenia; and *e*) other classes of patients including individuals with acute or chronic metabolic or vascular diseases. Factor analyses and analyses of variance of relevant groups have been made as independent checks on the factors isolated and identified in the above procedures. The resulting four-factor model of biological intelligence deserves the serious attention of neurophysiologists and neurochemists as a possible clue to the replication or redundancy of organized elements which may be characteristic of cortical mechanisms. For purposes of description and prediction, the variance on this battery of tests is grouped under such headings as 'judgment' (ability to organize recurrent elements into principles or categories), 'power' (the tonic energy or 'arousal' of the cortex), 'memory' (for over-all organization and form as well as for the details of place and relationship), and 'modality' (organized avenues of input and output for cortical information).

It is of interest that the yardstick or scale for biological intelligence is proving in various investigations to be relatively 'culture-free' and appears to bear directly upon the over-all adaptations of individuals involved in intellectually creative work.

## NATURE OF IMAGES

Plato was one of the first to note that the memory or image of an object looks just like the original object. In 1910 Perky (49) presented experimental evidence for this view. Her subjects were asked to imagine a series of individual objects as if seen on a screen. Unknown to the subject, an assistant projected an actual picture of the particular object very faintly onto the same spot on the screen. Twenty-seven adult observers mistook the faintly projected picture for their own images.

Normally, images or traces are less vivid or bright, less saturated, less intense and somewhat simplified as to content in comparison with percepts of real objects (57). Yet drugs such as mescaline, for example, can enhance the properties of the image to the point where confusion with actual percepts arises (as noted by Klüver).

### *Figural Aftereffects*

Prolonged inspection of a curved line, a bounded area or a patch of color produces aftereffects which distort the resulting trace in characteristic ways. For example, following prolonged inspection of a curved line, a straight line will be perceived as curved in the opposite direction, a bounded area appears smaller, a constant area recedes in space, a colored patch less saturated (33, 34). This effect may last for several minutes, hours or days. The aftereffect or overriding of subsequent percepts has been attributed to satiation, the nature of which remains obscure. It does appear to be a property of the neural pool which exerts its influence without the subject being aware of its presence (48). Its possible relation to after-discharge in brain wave activity is unknown.

## NATURE OF MEMORY

Memory is a process whereby organized time-space events are carried forward in time. This has been referred to as the 'time-binding' feature of the brain. So ubiquitous are the phenomena of learning throughout the animal kingdom that it has been difficult to conceptualize the nature of the recording process. In spite of a voluminous literature of experimental studies on the nature of learning, one psychologist has written recently: "It is a blot upon our scientific ingenuity that after so many years of search we know as little as we do about the physiological accompaniments of learning" (22). There is fairly general agreement that organized experience is somehow, somewhere represented in the nervous system as substantive memory 'traces.' There is virtually no agreement as to what order of anatomical or electrochemical event comprises the memory trace (9, 18, 28). Speculations concerning their possible nature are reviewed by Galambos & Morgan in Chapter LXI of this *Handbook*.

Katz & Halstead (28) have proposed the nucleoproteins, RNA, as a possible storage mechanism for the engram. Recent investigations of F. Morrell (personal communication) would appear to lend some support to this notion. He has obtained selective staining of nerve cells, stained for RNA, in an induced epileptic focus transferred homologously between brain hemispheres at a time rate compatible with 'learning.'

Experimental investigations of memory may be divided into those which attempt to describe necessary conditions for the development of a memory trace (including Pavlovian conditioning, operant conditioning, human learning), and those which attempt to trap the memory trace in time and space (ablation studies, drug effects, metabolic effects, transfer effects). It is impossible to review all of this work here but the following publications will prove helpful (22, 23, 32, 37, 57). There is no known way compatible with life by which an individual memory trace can, with certainty, be erased from the neural pool once it has been laid down. In studies based upon well-established artificial habits ablation may disturb the performance of organized acts, as Lashley (37) and others have shown; but in general, retraining usually reveals some savings or sparing of the original trace. Lashley has concluded from his programatic study of the problem that the motor cortex does not participate directly in the transmission of the trace pattern. Furthermore, there is no evidence that the transmission of impulses over well-defined isolated patterns from one part of the cortex to another is essential for performance of complicated habits. Citing his work on the rat and monkey, along with that of Sperry also on the monkey (53), Lashley concluded that the associative connections or memory traces of the conditioned reflex do not extend across the cortex as well-defined arcs or paths. "The evidence thus indicates that for sensory-motor habits of the conditioned reflex type, no part of the cerebral cortex is essential except the primary sensory area. There is no transcortical conduction from the sensory areas to the motor cortex and the major sub-cortical nuclear masses, thalamus, striatum, colliculi and cerebellum do not play a part in the recognition of sensory stimuli or in the habit patterning of motor reactions" (37).

It is known that specific memory traces may be unaltered through wide variations in body temperature in warm-blooded animals, through the diurnal cycle of sleep and wakefulness, through associated electrical stimulation of various parts of the brain, through electrically induced convulsions, through biochemically induced convulsions, and through wide variations in the systemic biochemical milieu. Clinical observations based upon humans, on the other hand, have repeatedly revealed selective losses of memory (the agnosias on the input side and the apraxias on the output side) associated with focal trauma, space occupying lesions or brain disease, including senility. It has been possible to evoke a verbal report of 'images' or 'memories' in approximately 30 per cent of the human brains stimulated electrically by Penfield and his associates to elucidate underlying epilepsy. However, the possibility exists that such evoked memories are 'leakage' effects associated with some epilepsies and not with others since they have never been observed during stimulation of a normal hemisphere.

An encouraging approach to the trace problem has been introduced recently by Myers (46, 47). Addressing himself to the problem of interocular or interhemisphere transfer of pattern discrimination in cats, Myers has made an interesting discovery. The afferent connections from each eye were restricted to the ipsilateral brain hemisphere in nine cats by surgical section of the crossed fibers in the optic chiasma. The cats were then trained to perform visual pattern discriminations with a mask covering one eye. When the mask was later shifted to the opposite eye, it was found that the discriminations could be performed correctly with the untrained eye (and hemisphere). In six additional cats, prepared surgically in the above

manner, sagittal transection of the corpus callosum was carried out. These cats were then trained to perform pattern discriminations with a mask covering one or the other eye. When a consistently high level of performance had been attained, the mask was shifted to the other previously unmasked eye, whereupon the performance dropped abruptly to a chance level with 7 of the 10 discriminations tested. The three deviant results were attributed by Myers to irrelevant generalization effects between the several discriminations taught through the separate eyes. The findings are in marked contrast with the high-level transfer of visual discriminations obtained with the corpus callosum intact.

Myers subsequently trained two of the cats with combined sagittal transection of the optic chiasma and of the corpus callosum completely conflicting discriminations with the two eyes. The learning with the second eye occurred with relative ease and resulted in no disturbance in performance with the first eye. This finding also contrasts markedly with the performance of cats with intact corpus callosum.

These results seem clearly to implicate the corpus callosum in the integration of the two hemispheres in visual learning and transfer of the memory traces. It is possible that Myers has opened the door to a formidable assault upon the memory trace problem. Through ingenious use of combined surgical and training procedures, he has demonstrated that it is possible to trap specific memory traces in one hemisphere. He is now in a position to explore systematically the relevant details of the structures involved. Is the grain or mass necessary for establishing the initial training of one hemisphere exactly homologous with that of the other hemisphere which is receptive in the trace-transfer transaction? In other words, how much of each hemisphere can be eliminated surgically or otherwise without disturbing trace transfer? Are the functional islands of tissue different chemically or ultrastructurally in the receptive and unreceptive transfer states? It seems likely that these are but some of the answerable questions opened up by Myers' investigations.

## MAINTENANCE OF HOMEOSTASIS IN THE CENTRAL NERVOUS SYSTEM

Unlike electrical and mechanical machines which are addressed both as to program and operating energy level, the brain is capable of spontaneous periodic and aperiodic changes in state. Perhaps the most dramatic example of this is afforded in the many intermediate states between deep sleep and high wakefulness emphasized by Kleitman (30) and Hess (21). Bremer (7) points out that "the cerebral cortex participates actively in its own arousal and in the maintenance of its waking state by the corticofugal impulses which it sends to the brain stem reticular formation." He suggests that the act of falling asleep is triggered by the cumulative deactivation or defacilitation of the encephalic neural networks resulting from synaptic fatigue and favored by a reduction in the exteroceptive and proprioceptive sensory afflux. Jasper (27) fractionates the reticulothalamocortical projection system into diffuse unspecific pathways, regional unspecific pathways and localized specific pathways. It is not yet possible to state whether any or all of these is directly involved in the defacilitation called sleep, nor is it yet clear to what extent changes in peripheral tone, with associated afferent feedbacks, is primary or secondary in the state of sleep. Sherrington (51), Freeman (11, 12) and others are responsible for the observation that muscle tonus waxes and wanes in parallel with mental efficiency, being lowest at waking, rising rapidly during the early morning, declining again in the afternoon and reaching a new peak during the evening hours. Freeman has found that motor tension increases during the execution of a task and drops when it is completed. He concludes that motor tension must be higher under fatigue or distraction in order to maintain a normal level of mental work. In this latter connection Bills (3) and Stroud (54) found that a moderate degree of constant pressure on a dynamometer facilitated the learning process for paired associations and lists of nonsense syllables. It is difficult to visualize how tonic influences per se, particularly in unrelated muscle groups, could affect favorably the learning process. However, relatively diffuse or regional nonspecific afferent feedbacks to the neural pool might serve a general facilitating function. Segmental effects of muscle relaxation were explored by Jacobson & Carlson (26) who found that sufficient relaxation could abolish the knee jerk in man. It is of interest that Miller (45) found that subjects in relaxed states reacted to electrical shock with reduced amplitude and speed of reaction. In contrast with normal tonic levels, the subjects reported under relaxation an apparent decreased intensity of sensation induced by the shock.

The discovery of the reticular activating system by Magoun, Lindsley, Morruzzi, Jasper and others has in a few short years had a far-reaching influence upon brain research. Physiologists have been somewhat

prompt in assigning functions previously ascribed to the cortex to this system. That it supplies a facilitating or nonspecific tonic influence upon the neural pool along the line suggested in 1947 by Halstead's Power Factor (15), and in commentary by Lashley in 1954 (38), seems reasonably well established. There is, however, serious question, from experimental evidence thus far presented, that this system controls more than relatively gross changes in state of the brain as opposed to the vernier settings of the system demanded by the precise contingencies of behavior within and across modalities of input and output. Halstead's measures of biological intelligence appear to tap the vernier sets of the brain in man and are selectively disturbed by primary lesions of the cortical mantle.

Recent studies of spontaneous and stimulus-evoked responses of the autonomic nervous system by Lacey & Lacey (35) raise the possibility that the Power Factor or 'energizer' of cortical mechanisms may in part be supplied by the autonomic system. The suggestion by these authors that an autonomic response becomes a stimulus with feedback via visceral afferents and reticular formation, or via the baroreceptors, is worthy of serious exploration.

## SUMMARY

It is clear that only the merest beginning has been made in man's attempt to unravel the details of relationship between higher brain functions and specific neural mechanisms. Analysis of the thinking process reveals that it is basically a form of problem-solving behavior which involves the correlation and integration of critical events in time and space. There are five steps or stages in the programing of thinking behavior which enable us to see more clearly than the gestaltists, for example, the essential distinctions between perception and thinking. The programing of these five stages is crucial for the emergence of scientific explanation or rational solution of problems.

The coefficient of correlation and factor analysis represent mathematical tools, evolved in other contexts, for nonverbal analysis and communication of thinking behavior. Likewise, the recently developed technique in neurophysiology of autocorrelation and cross-correlation of information obtained directly from the neural pool promises to carry our understanding beyond the barrier of words.

As better scientific questions are raised and defined, brain chemistry may be expected to supply the missing sources of variance.

Images or memory traces are the proof of experience. As the building blocks of mind, they exert a coordinating, stabilizing and filing function for the 'old' against which the 'new' is tried. Their specific neurology is little understood, but recent experiments which appear to have trapped them in the laboratory give promise of elucidating their specific dependencies upon neural structures.

## REFERENCES

1. Adrian, E. D. *The Physical Background of Perception*. Oxford: Clarendon Press, 1947.
2. Barlow, J. S. and M. A. B. Brazier. *Electroencephalog. & Clin. Neurophysiol.* 6: 321, 1954.
3. Bills, A. G. *Am. J. Psychol.* 38: 227, 1927.
4. Boring, E. G. *A History of Experimental Psychology*. New York: Century, 1929.
5. Brazier, M. A. B. and J. U. Casby. *Electroencephalog. & Clin. Neurophysiol.* 3: 375, 1951.
6. Brazier, M. A. B. and J. U. Casby. *Electroencephalog. & Clin. Neurophysiol.* 4: 201, 1952.
7. Bremer, F. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer and H. H. Jasper. Springfield: Thomas, 1954.
8. Chapman, L. F., D. Symmes and W. C. Halstead. *J. Comp. & Physiol. Psychol.* 48: 421, 1955.
9. Eccles, J. C. *The Neurophysiological Basis of Mind*. Oxford: Clarendon Press, 1952.
10. Fearing, F. *Reflex Action. A Study in the History of Physiological Psychology*. Baltimore: Williams & Wilkins, 1930.
11. Freeman, G. L. *J. Gen. Psychol.* 4: 309, 1930.
12. Freeman, G. L. *Psychol. Rev.* 38: 428, 1931.
13. Goldstein, K. *The Organism*. New York: Am. Bk. Co., 1939.
14. Halstead, W. C. *Am. J. Psychiat.* 96: 1263, 1940.
15. Halstead, W. C. *Brain and Intelligence*. Chicago: Univ. Chicago Press, 1947.
16. Halstead, W. C. In: *Symposium on Physiological Psychology*, edited by R. Trumbull. Pensacola, Fla.: Off. Naval Res., 1955, p. 259.
17. Hanfmann, E. and J. Kasanin. *J. Psychol.* 3: 521, 1937.
18. Hebb, D. O. *The Organization of Behavior*. New York: Wiley, 1949.
19. Heidbreder, E. *J. Gen. Psychol.* 24: 93, 1947.
20. Herrick, C. J. *The Evolution of Human Nature*. Austin: Univ. Texas Press, 1956.
21. Hess, W. R. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer and H. H. Jasper. Springfield: Thomas, 1954.
22. Hilgard, E. R. *Theories of Learning*. New York: Appleton, 1948.
23. Hilgard, E. R. and D. G. Marquis. *Conditioning and Learning*. New York: Appleton, 1940.
24. Hull, C. L. *Psychol. Monogr.* 28: 1, 1920.
25. Jacobson, E. *Am. J. Psychol.* 44: 677, 1932.

26. Jacobson, E. and A. J. Carlson. *Am. J. Physiol.* 73: 324, 1925.
27. Jasper, H. H. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer and H. H. Jasper. Springfield: Thomas, 1954.
28. Katz, J. J. and W. C. Halstead. In: *Brain and Behavior*, edited by W. C. Halstead. Berkeley: Univ. California Press, 1950, p. 1.
29. Kellogg, W. N., W. B. Scott, R. C. Davis and I. S. Wolf. *J. Comp. Psychol.* 29: 43, 1940.
30. Kleitman, N. *Sleep and Wakefulness*. Chicago: Univ. Chicago Press, 1939.
31. Klüver, H. *Genet. Psychol. Monogr.* 1 (2): 69, 1926.
32. Köhler, W. *Gestalt Psychology*. New York: Liveright, 1929.
33. Köhler, W. and D. A. Emery. *Am. J. Psychol.* 60: 159, 1947.
34. Köhler, W. and H. Wallach. *Proc. Am. Phil. Soc.* 88: 269, 1944.
35. Lacey, J. I. and B. C. Lacey. *A. Res. Nerv. & Ment. Dis., Proc.* In press.
36. Lacey, J. I. and R. L. Smith. *Science* 120: 1045, 1954.
37. Lashley, K. S. *Symp. Soc. Exper. Biol.* 4: 454, 1950.
38. Lashley, K. S. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer and H. H. Jasper. Springfield: Thomas, 1954.
39. Lesse, H. *Fed. Proc.* 16: 79, 1957.
40. Maier, N. R. F. *J. Exper. Psychol.* 35: 349, 1945.
41. Malmo, R. B., C. Shagrass, D. J. Belanger and A. A. Smith. *J. Abnorm. & Social Psychol.* 46: 539, 1951.
42. Malmo, R. B., C. Shagrass, J. F. Davis, R. A. Cleghorn, B. F. Graham and A. J. Goodman. *Science* 108: 509, 1948.
43. Max, L. W. *J. Comp. Psychol.* 19: 469, 1935.
44. Miller, G. A. *Language and Communication*. New York: McGraw-Hill, 1951.
45. Miller, M. *J. Exper. Psychol.* 9: 26, 1926.
46. Myers, R. E. *J. Comp. & Physiol. Psychol.* 48: 470, 1955.
47. Myers, R. E. *Brain* 79: 358, 1956.
48. Osgood, C. E. and A. W. Heyer. *Psychol. Rev.* 59: 98, 1951.
49. Perky, C. W. *Am. J. Psychol.* 21: 422, 1910.
50. Reitan, R. M. *A.M.A. Arch. Neurol. & Psychiat.* 73: 28, 1955.
51. Sherrington, C. S. *The Integrative Action of the Nervous System*. London: Cambridge, 1906.
52. Smoke, K. L. *Psychol. Monogr.* 42: 1, 1932.
53. Sperry, R. W. *J. Neurophysiol.* 10: 275, 1947.
54. Stroud, J. B. *J. Exper. Psychol.* 14: 184, 1931.
55. Symmes, D. S., L. F. Chapman and W. C. Halstead. *J. Acoust. Soc. Am.* 27: 470, 1955.
56. Thurstone, L. L. *Multiple Factor Analysis*. Chicago: Univ. Chicago Press, 1947.
57. Woodworth, R. S. *Experimental Psychology*. New York: Holt, 1938.

# The patterning of skilled movements

JACQUES PAILLARD | *Faculté des Sciences, Université d'Aix-Marseille, Marseille, France*

CHAPTER CONTENTS



THE TERM 'SKILLED' is employed with various meanings. We shall use it here to designate among motor activities a particular category of finely coordinated voluntary movements, generally engaging certain privileged parts of the musculature in the performance of various technical acts which have as common characteristics the delicacy of their adjustment, the economy of their execution and the accuracy of their achievement.

Such movements belong to the category of the so-called manipulative activities and have to be set apart from purely locomotor activities. The skillful use of certain motor organs for gripping and transforming matter is included in the scale of evolutionary development which leads from the primitive activities of prehension to the more complex activities of manipulation, finally culminating in the achievement of manufacture which is the outcome of human dexterity (137). 'Manipulation' (like 'manufacture') designates etymologically the work of the hand; 'dexterity' characterizes, in its original sense, the quality of these skilled actions which are executed by the right hand (and consequently better than by the left hand). Such anthropomorphism in the vocabulary indicates the very particular and privileged role of the human hand as the most elaborate instrument for skilled activities.

Indeed, phylogenetic considerations will show how the human hand, in spite of the bonds which tie it to the animal world, behaves (as does, in another field, the very special apparatus of language expression) in accordance with an absolutely original functional formula. Ever since their origin, the functional organization of living creatures has been characterized by a very harmonious coordination between the apparatus for collecting information thanks to which the organism can construct its knowledge of the surrounding world, the locomotor arrangements which permit it to explore and the organs of prehension which condition its acquisition of food.

Among the nonsessile organisms, for which the exploratory activities become predominant, the organization of the functional components appears identical; the organs for prehension and for securing of information are grouped at the anterior part of an

elongated body while the entire posterior part consists of organs of locomotion enclosing the visceral cavity.

It is in this cephalic area, served by the apparatus of prehension, that the first forms of specialized technical activity will develop. The major use of these technical operations is at first alimentary in character: the capture of prey, its seizure and the dissection of the food.

The appearance of locomotor appendages symmetrically disposed along a longitudinal axis is soon accompanied by adaptation of the most anterior elements of this mechanism to aid the organs of prehension of the buccal region.

The evolution of vertebrates, and especially that of mammals, is marked by a simultaneously synergic and competitive interpenetration of the motor apparatus of prehension and that of locomotion. Thus, in the herbivorous mammals, the anterior members lose all integration with the cephalic region. This fact seems to favor the development of facial tools: the ruminants' specialized incisors, the elephants' tusks, nasal and frontal horns, extensive lips, trunks, etc.

Other mammals, on the contrary, which have kept the five-fingered hand of the primitive reptiles use the anterior members for technical purposes. This appears in various stages of development in a great number of species, the functional organization in which is often without direct relation to their taxonomic positions. Each group offers examples of species utilizing the anterior members for technical purposes. The least favored are the species specialized for rapid locomotion as, for instance, the hare as compared with the beaver among the rodents. The technical use of these anterior locomotive appendages by these species is accompanied by a particular postural evolution, the acquisition of a sitting position which liberates the anterior members and facilitates their technical activity (109).

The most favored are the primates which show the highest level of appendicular technical facility. The particular form of locomotion that is imposed on the monkey by arboreal life is accompanied by a transformation of the four extremities into perfected organs of prehension; as Broca (18) remarked, "The monkey is more a quadruman than a quadruped." The tail itself becomes a real organ of prehension. Conjointly with this evolution of appendicular technical skill, there has been progressive erection of the vertebral column in the sitting position.

The essential feature marking the transition from the monkey to man is the locomotive arrangements of the latter. The human foot presents an evolution of the same order as that of the quadruped mammals which use their four limbs exclusively for rapid locomotion. In contrast, the hand evolves definitely in the prehensile sense.

Thus this evolution is marked, from the anatomical point of view, by a definite liberation of the anterior members from servitude to locomotion by the erection of the vertebral column to the vertical position. The gain in power of the hand brings about a parallel regression of the organs of facial prehension. The skull is then liberated from its duties of mechanical support for the apparatus of mastication on the vertebral column. It may then increase in size (71). From the functional point of view, this evolution results in the nearly total predominance of the hand in technical acts, a nearly complete liberation of the buccal organs so that they may become available for the development of new motor mechanisms of expression, and an increase in the volume of the brain in an enlarged cerebral cavity.

The neuromotor system has evolved in relation to this change in body relations. Whereas the locomotive functions have remained dependent upon subcortical centers, the development of motor activities of technical character appear to have been intimately associated with expansion of the motor areas in the neocortex.

In the species in which facial behavior is prominent, there exists an extensive cortical sensorimotor 'representation' of the anterior facial region. The progress of the technical proficiency of the anterior locomotive appendages is accompanied by a progressive extension of the cortical sensorimotor representations of these regions, particularly for their distal parts. The area and the density of the corresponding cellular fields increase in proportion to the complexity and the delicacy of the movements which they control. The largest fields correspond to the organs most frequently engaged in technical operations: the lips, the tongue and the distal portions of the anterior limbs (1, 38, 136).

In the monkey, the 'representation' of the digits (notably the thumbs) and of the tail take on considerable importance. Man possesses an extensive 'representation' of the hand, with predominance of the thumb, then of the second and the fifth digits, whereas the inferior member is poorly 'represented,' as shown in figure 1.

It is significant to notice here that, in spite of the apparent regression of facial technical capacity in

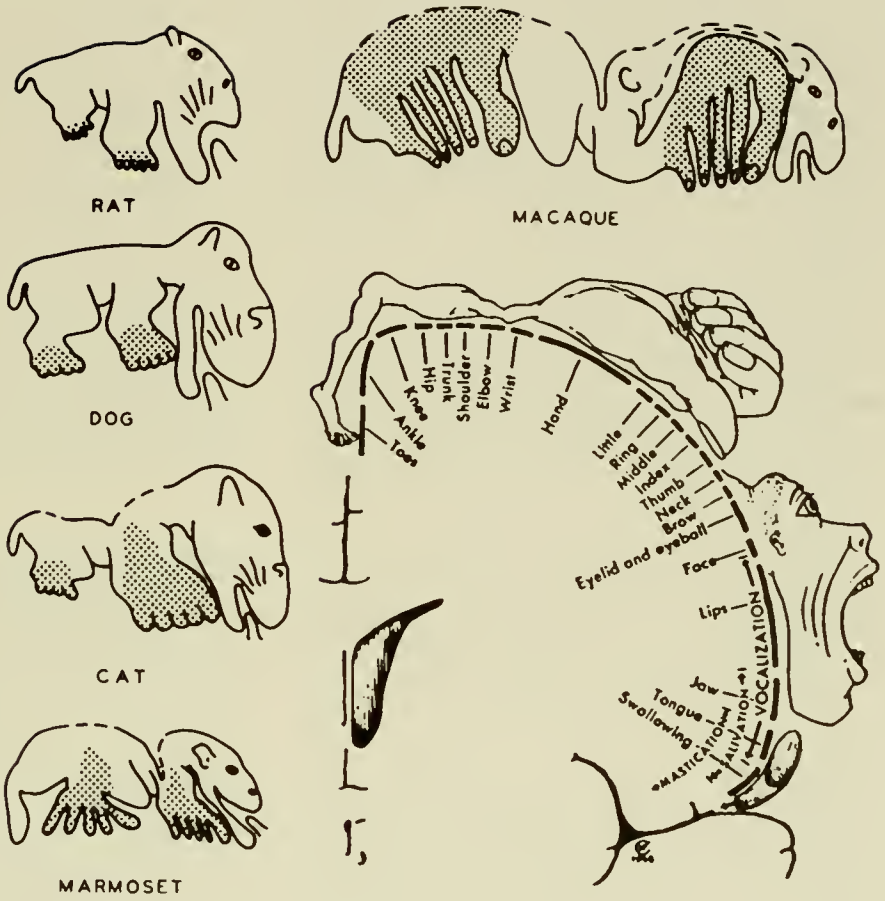



FIG. 1. *Left and upper right:* Evolution of the pattern of localization in the postcentral tactile area as defined in a series of mammals. The *dotted areas* show the extent of the areas devoted to hand and foot. The figures are not all to the same scale, but the proportions of each are approximately correct. [From Woolsey (136).] *Lower right:* Motor sequences in the Rolandic cortex of man shown on a coronal section of the hemisphere. The length of each *block line* in the cortex indicates the comparative extent of the representation of movement of each part aroused by electrical stimulation of the corresponding cortical area. The importance of the hand, as shown in the homunculus, is to be noted. [From Penfield & Rasmussen (96).]

relation to the activities of prehension, the motor centers of the face have kept an importance equal, at least, to that of the hand. This fact is related to the development of a new and unprecedented facial function, the emission of organized sounds which constitute the complex phonetic expression of man. (Specialized motor areas also are associated with the control of ocular movement in relation to the perfecting of binocular vision.)

One of the more significant outcomes of this evolution is the development of new nervous pathways connecting the cortical centers of command with the peripheral motor organs. The appearance followed by the development and the perfecting of the pyramidal system in the vertebrates (69) is directly related to the refinement of control of the muscle groups most used in the expression of skilled movements. We shall come back later, and more extensively, to this point.

This picture of phylogenetic evolution is confirmed, on the whole, by the course of human ontogenesis: the progressive development from motor activities consisting of prehension and specifically buccal exploration to the ever more preponderant utilization of the hand, the potentialities of which are manifested in strict relationship to the delayed and progressive maturation of the pyramidal system.

In this ontogenetic evolution there likewise appears a strict functional synergy uniting the system of prehension with the system for securing information (first cutaneous, then essentially visual) and with the mechanism for locomotion with progressive erection of the body's axis and the liberation of the superior members by assumption of the standing position.

To this progress contributes, to an important degree, the prodigious elaboration of human mental activity. The human privilege of 'motility of manufacture' undoubtedly depends, in part, upon the mechanical advantages of the human hand and upon the refinement of the nervous mechanisms of command which evoke its action; but it is due, above all, to the immense psychical possibilities of which it is the slave and on which, in return, it confers

further means of action. "The wealth of sensibility, the control of binocular vision, the progress of intelligence and of creative imagination, the tenacity of purpose, all converge towards the realization of this admirable tool to which, from the time of Hippocrates, Aristotle and Galen up to the present day, philosophers, doctors, physiologists and psychologists and also the most meditating laymen have directed their thoughts . . . " (118).

These preliminary considerations, inspired by the data of phylogenesis and ontogenesis, help us to realize the unique place held by skilled movements among the forms of expression of motor capacity and the ties that bind their neurophysiological study to that of the higher functions of the nervous system.

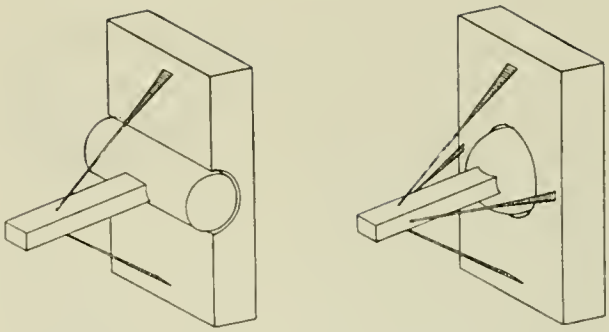


FIG. 2. Models of joints. *Left:* A hinge joint, with a single degree of freedom, moved by a pair of antagonistic muscles. *Right:* A ball joint, with free rotational motion, operated by four muscles. [From Weiss (130).]

## PERIPHERAL EXPRESSION OF SKILLED MOVEMENTS

We shall try, as a first step, to describe the conditions and the forms of expression of skilled movements at the level of the peripheral organs.

### *Conditions of Expression*

Movement is the result of the motor activity of the muscles acting upon the levers of the skeleton. The morphology of the effector organ sets the mechanical conditions which limit the possibilities of its use. From this point of view, man's hand is, as Galen said, "a perfectly constructed instrument of prehension." We owe to this author a penetrating study of the mechanical conditions of the act of prehension. The essential morphological characteristic of the hand of the primates and of man resides in the rather complete mechanical independence of the five digital appendices which compose it and still more in the opposition of the thumb. Aristotle, who called it the 'great finger,' underlined the functional importance of this arrangement. Galen noticed, with exactitude, the advantage of man's hand with its opposable thumb over the flat hand of the monkey.

Thirty muscles are employed in the movement of the multiple joints of the hand. As stressed by Jackson (116), they make possible the thousands of combinations of movements which he believed to be 'represented' in the cortex. We must note especially with Gratiolet [cited by Alix (5)] the addition to the hand of a muscle belonging only to man, the long proper flexor of the thumb, the independent action of which permits the isolated flexion of the second phalanx and contributes to the execution of the delicate movements of writing (28).

Each contracting muscle generally exerts an obvious mechanical effect which is due to its fixed attachment to the bone lever. The arrangement of muscles relative to the lever arms shows several different types of organization. The most elementary organization appears in the play of the hinge joint articulations, the 'ginglymi' of Winslow (134), as in the knee, elbow and interphalangeal joints. The mobility of such a joint requires the insertion of two muscles or muscle groups on opposite sides of the bone lever (see fig. 2). The simultaneous action of these two muscles ('coinnervation') permits fixation of an articulation and its maintenance in a determined position by means of a nonkinetogenic muscular activity (which had already been called 'tonic' by Galen). From the antagonistic action of these muscles ('reciprocal innervation'), one contracting while the other relaxes, there results a movement of the lever. In relation to the natural position of rest of the lever arm, we call the muscle the contraction of which tends to augment the open angle of the articulation an 'extensor,' and the one the action of which diminishes this angle a 'flexor.'

The hinge joint articulations are, however, not the rule. The joints of the segments of the limbs and of their attachments to the skeletal girdles generally possess more than one degree of freedom, the 'arthrodies' and 'enarthroses' of Winslow (134). Accordingly, they require for their movement a more complex muscular organization than the simple antagonism just described.

The 'ball joint' can, for instance, be moved in any direction whatsoever around its center within its

angular cone of action (see fig. 2). This action is mediated by a series of muscles acting in the several planes. From the combination of various active muscles and their relative intensity of contraction there results an infinite variety of possible positions of the lever arm. Aside from the hinge joints of the metacarpals and between the phalanges which give more rigidity to the digitals, the articulations of the fingers, of the thumb and of the wrist are ball joint articulations with all their multiple possibilities.

It becomes difficult, in the presence of such an organization, to justify the classic dichotomy between the agonist and the antagonist muscles required by a rigid adherence to the principle of reciprocal innervation. The only cases in which this convenient distinction is justifiable are those of the hinge joints.

Every movement results from the cooperative action of a number of muscles. "An isolated muscular action does not exist in nature," exclaimed Duchenne de Boulogne (28), observing for the first time the effects of 'localized electrization' in man and noting the lack of gestural significance of the movements produced by this method.

Winslow (134) has the merit of having clearly expressed the necessity for complex cooperation of muscles to "move a part of the body or to hold it in a determined position." The analysis by this great anatomist led him to propose a functional classification of the divers muscles implicated in a particular action, according to the nature of their participation. *a*) The 'principaux moteurs,' later named 'prime movers' by Beevor (9), which directly carry the movement to the determined situation or attitude. *b*) The 'moderateurs' which moderate or counterbalance the action of the former, Beevor's 'antagonists.' *c*) The 'directeurs' which stabilize the action laterally. Beevor distinguished 'synergists' which cooperate directly with the prime movers and 'fixers' which stabilize the articulations involved.

### *Forms of Expression*

It is to Duchenne de Boulogne (28) that we owe the first precise description of certain basic motor figures which underlie the execution of our movements. He underlined the 'obligatory and imperative' character of these 'instinctive reactions,' which are stereotypes embedded in the heritage of the species and associated with the most habitual modes of utilization of the organ of movement concerned. We may cite as an example the synergic action of the fixing muscles of the proximal articulations of the limbs; without the firmness of this rigid prop, the delicate adjustments of the distal articulations could not be efficiently effected. Clinical experience reveals that simple paralysis of the radial muscles which contribute to the fixation of the wrist is sufficient to interfere with the prehensile activity of the fingers.

The first electromyographic recordings were made in the course of the investigations of Wachholder (124) and of Altenbürger (6). These workers have made available a more refined method of analysis of muscle patterning. Wachholder (124) insisted upon rhythmic alternation of the activity of the antagonists as being, under optimal conditions, the most economical form of activity. Altenbürger has provided experimental support for the hypothesis that there is a preformed central structuring of the pattern of synergic activity. The quasisimultaneity of innervation of the diverse muscular groups would appear to exclude the existence of a reflex regulation originating in the contraction of the muscle moving first (6).

The polygraphic electrophysiological methods now available are well adapted to the study of the patterns of muscular activity. They have revealed the astonishing complexity of the organization of the most simple acts. This is illustrated by the very accurate work of Tournay & Fessard (119) at the level of the motor unit which shows the extreme subtlety of these synergic innervation patterns (see figs. 3, 4). To patterning of spatial distribution which determines the participation and the degree of intervention of the diverse muscles implicated in the action is added an extremely complex patterning of temporal succession. The 'kinetic melody' is organized according to the sequences required by a most precise orchestration which defines the participation of each performer (see fig. 4).

We must note here the necessity of avoiding the common confusion of the prime mover, in the sense used by Beevor (the 'principal moteur' of Winslow), with the muscle moving first in the beginning of an action. The analysis clearly reveals that the excitation of a cooperating part often precedes in time the excitation of the muscle primarily responsible for the movement.

The most significant fact revealed by this type of analysis of muscular activity is the extreme fluidity of the patterning of action, depending on the initial posture of the segments and on the nature of the resisting forces. The same final effect can be attained

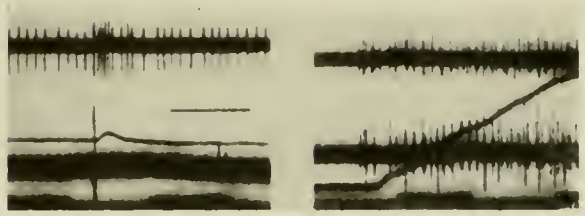


FIG. 3. Electromyographic analysis of the synergy between the proper flexor of the index and the extensor carpi radialis. *Left: Upper line*, activity of the extensor carpi radialis which shows the tonic functioning of a motor unit as detected by the coaxial needle. *Third line*, activity of the flexor muscle. *Second line*, the mecanographic record showing a very slight movement of flexion of the index with the corresponding activity of the flexor muscle (grouped discharges of few motor units). The corresponding synergistic activity of the extensor carpi is shown in the phasic increase of the frequency of discharges of the active unit. *Right:* Same conditions, but the two muscles are initially silent. The index finger is progressively extended as shown by the *mechanographic record*. Note the simultaneous start of the activity in the two muscles and the recruiting of new units as the movement progresses. [From Tournay & Fessard, unpublished observations.]

in a hundred different ways. A given movement can never be reproduced identically. We can never find two patterns of activity repeated twice in succession which are strictly superposable. At the level of the muscle itself the spatiotemporal pattern of recruitment of the motor units implicated in a voluntary movement is never absolutely identical.

The innate mechanisms involved in fundamental synergic action no longer appear to have the imperative and rigid form that Duchenne de Boulogne assigned to them. The studies of Livingston *et al.* (78) on the synergic action of the radial muscles involved in the flexion of the fingers of the hand reveal the extreme plasticity of the play of these 'instinctive associations.' The radial muscles behave in different ways, adapting themselves to the changing circumstances of execution of the movement. They may even be completely relaxed when their action would be mechanically superfluous. Winslow (134) had already noticed this 'economical aspect' which characterized the intervention of the muscles which accompany a movement. "In certain cases, the moderators do not act at all, their action being supplied by the foreign resistance or only by the weight of the part to which they are attached."

The problem of patterning of skilled movements confronts us here in all its bewildering complexity, particularly when we undertake to study the reactions of an entire organism where each partial mechanism is dependent upon the functioning of the whole. This complexity helps us to anticipate that, among the neurophysiological mechanisms brought into play in such operations, there will be included components of a high level, psychological as well as reflex, some acquired by learning as well as others which are congenital.

The problem of the neurophysiological basis of the patterning of skilled movements must be defined here in terms of 'coordination.' Following Weiss (130) we mean by coordination "the selective activation of definite groups of units in such combination that their united action will result in an organized peripheral effect that makes sense. . . ."

We can already begin to see, in the light of this first analysis, that the problem of nervous coordination can no longer be stated in the simple form, classically accepted, of an innervation exerting antagonist effects on the extensor and flexor muscle groups. We must seek for a mechanism which can select a privileged combination of muscles from among a considerable variety of possible combinations.

In this connection, two fundamental questions

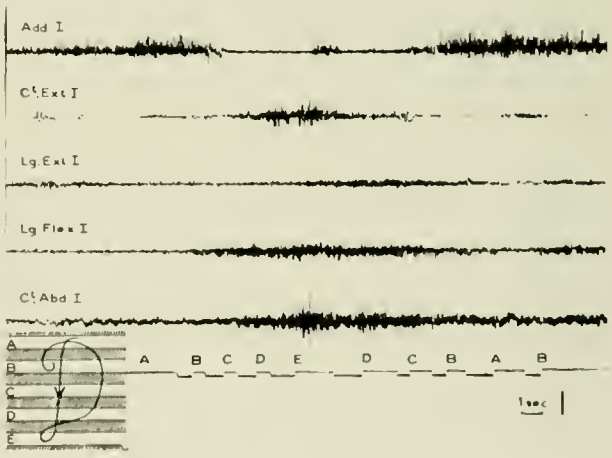



FIG. 4. Pattern of activities of the muscles of the thumb in a writing movement. Electromyographic activity is detected by means of five coaxial needles from the following muscles: *Add. I*, adductor policis; *Ct. Ext. I*, extensor brevis policis; *Lg. Ext. I*, extensor longus policis; *Lg. Flex. I*, flexor longus policis; and *Ct. Abd. I*, abductor brevis policis. The subject, in a normal writing posture, is asked to follow the contour of a letter 'D,' drawn on a metallic plate, with a metallic stylus. The current going from the stylus to the plate is switched off when it passes across regularly arranged isolating horizontal bands. Thus, the *lower line* of the record relates the different phases of the movement with the activity of the muscles. (From Tournay & Paillard, unpublished observations.)

arise: what are the factors which determine the choice of the muscles to be engaged in a given movement and the variable spatiotemporal ordering of their activation, and how does this selective operation operate in the nervous system. We shall look first for the elements required to answer the second question.

## EXECUTIVE PATHWAYS OF SKILLED MOVEMENTS

Pathological data, as well as the more precise findings of animal experimentation, agree in emphasizing the role of cortical mechanisms in subserving this kind of finely discriminative muscular activity.

The careful studies of Tower (120), Hines (51) and others on monkeys with lesions of the pyramidal system, which were reviewed by Tower (121) in 1949, have shown the essential part played by the corticomotoneural tracts in conveying the nervous messages that appear to be strictly necessary for the evocation of skilled movements. Although impaired in various degrees by disturbances in other parts of the nervous system, the ability to perform skillful acts appears to be definitely lost after interruption of this direct pathway between the cortex and the peripheral effectors.

Since the work of Hughlings Jackson (116), the concept of a hierarchical functional organization of the nervous structures has become familiar. As a matter of fact, when we try to identify the nervous structures implicated in the expression of skilled movements, two levels immediately command our attention. At the lower level we find in the medulla oblongata and spinal cord groups of motor neurons which hold the peripheral organs under their direct control (Jackson's first level). At the cortical level are located the structures in which are assembled the neurons of origin of the pyramidal paths (Jackson's second level).

Both of these levels present a remarkable somatotopy of organization. The existence in these two regions of topographically ordered keyboards challenges us to search for the meaning of such a structural arrangement in relation to the spatial patterning of effector commands.

### *The Lower Motoneuron Keyboard*

The relative accessibility of the spinal structures early made these regions favored grounds for neurophysiological experimentation. Following the path opened by Sherrington, our knowledge of the anatomical and functional organization of these structures has progressed considerably. The study of reflex activity of the spinal cord has contributed very largely to the establishment of the fundamental basis upon which our conceptions of nervous mechanisms are constructed. Each muscle is found to be associated with a contingent of motoneurons grouped in the ventral part of the spinal grey matter according to a rather strict topographical distribution. The motoneuron, with the muscle fibers that receive its axonic terminations, forms the functional unit of the spinal keyboard. It is the 'motor unit' as defined by Sherrington (108). In normal functional conditions each impulse of a motoneuron evokes in the corresponding muscle bundle a synchronous contraction of its components (65). This apparent rigidity of organization of the motor unit does not exclude a great suppleness in the function of the basic mechanism.

At the level of the motor units, the intensity of the mechanical effect resulting from neuronal discharge evidently depends not only on the number of muscle fibers simultaneously brought into play (Sherrington's ratio of innervation), but also on the frequency of the impulses. Due to the viscoelastic properties of muscular tissue, the resulting mechanical effect will increase with the frequency of the impulses. The optimum effective rhythm is of the order of 50 per sec. (tetanic fusion). The unit develops under these conditions a tension which is five to six times that developed in a single twitch. At the level of the muscle, the cooperative action of the various motor units offers a complementary means of gradation of contraction through recruitment of motor units in an ever increasing number. The most favorable conditions for the cooperative activity which assures subtle and nuanced mobilization of the effector organ results, as has been shown, from the asynchronism in the activation of the motoneurons.

In other words, the time and intensity characteristics of muscle contraction depend on the timing of the activation of the several units of the motoneuronal keyboard (temporal dispersion), on the proportion of active to inactive units and on the frequency of their discharges.

It is noteworthy that the anatomical arrangement of the segments most usually engaged in the execution of skilled movements, the distal part of the members, undergoes an increase in the number of the muscles moving the mobile parts accompanied

by a reduction in their size. At the same time, the innervation ratio of the motor units which compose the muscle tends to increase (a single motoneuron controlling a smaller number of muscle fibers). The delicacy of control is thereby increased.

The activation of motor units therefore must conform to the spatiotemporal patterning which bears an effective relationship to the functional characteristics of the peripheral organ. This patterning depends simultaneously upon the heterogeneity of the threshold of excitability of central elements and upon the modulating actions of central elements which contribute to the creation of the 'central excitatory state' (107).

The concept of the motoneuron as a 'final common path' for actions of various origins (Sherrington) finds support today in our knowledge of the elementary mechanisms of synaptic transmission. These permit us to understand the subtle integrations which take place in the somatodendritic membranes. A fine modulation of the state of reactivity of the motoneurons depends upon competition of the facilitating and inhibitory influences exerted in the regions of synaptic influence. The study of the reactivity of motoneurons in reflex activity has revealed the graded mode of expression of certain predetermined configurations of influences. The mechanisms mediating tonic postural regulations, for instance, are capable, as we know, even in the absence of higher control, of executing harmonious chords of postural orchestration upon the spinal keyboard without confusion, but lacking in originality.

Thus, the spinal keyboard does not receive the commands from higher levels as a docile instrument ready to transmit, blindly and faithfully, carefully prepared orders to the muscles. It appears as a fine machinery sensitive to certain types of influences, influenced by messages of diverse origins which, directly or indirectly by way of the internuncial systems, converge upon it. It already constitutes in itself an 'integrative' structure in the sense that Sherrington gave to this term (107). This structure interprets the orders that it receives and transmits them only as a function of an ever changing state of receptivity.

### *The Upper Motoneuron Keyboard*

Under the inspiration of Sherrington, data relative to the spinal keyboard emerged progressively and clearly from the research; by contrast, the studies relative to the organization of the cortical motor area have encountered many difficulties. The interpretation of these results, even until recently, has been the subject of numerous and sometimes passionate controversies (128).

After the first observations by Jackson (116), the experimental studies of Fritsch & Hitzig (37) and of Ferrier (33) made it clear that in the region anterior to the central fissure there exists some mode of 'representation' of movements evocable by electrical stimulation of the cortical tissue. Leyton & Sherrington (72), by means of punctate electrical stimulation of the motor cortex with just supraliminal intensities in the monkey, obtained a regional 'representation' of the various parts of the body.

The existence of such a somatotopic organization of the so-called motor area has been confirmed by all investigators. However, the diversity and the instability of the results obtained with direct electrical stimulation of the cortex lead to a rather confusing polemic; this has been discussed by Bucy (20) and by Walshe (128).

Certain authors following Foerster (35), and more recently Woolsey (135) and Hines (52), advocate a precise somatotopy which extends not only to the muscular groups of a same region of the body, but to the muscles themselves. This concept embodies the so-called 'mosaic' interpretation of cortical somatotopy. As in the spinal keyboard, each region contains the groups of pyramidal neurons the stimulation of which evokes the response of a given muscle.

For other authors, inspired by the ideas of Jackson, the cortical representations are functional. Movements and not muscles are represented in the ascending frontal convolution. Jackson picturesquely described this by saying that the motor cortex "thinks in movements, not in muscles." According to this concept, a muscle, or a fraction of a muscle, must be represented as many times as there are types of movements employing that muscle, hence the idea of a multiplicity of 'representations' of the muscles.

It seems today that in the light of the most recent studies (22, 97) we are drawing near to a satisfactory interpretation of the contradictions of past experiments using electrical stimulation of the cortical areas. We are now able to appreciate the number and the importance of the difficulties encountered in the study of cortical motor function. These include: *a*) the extreme difficulty of systematization and interpretation of pathological data; *b*) the morphological complexity of the structure exposed to the artificial influence of direct electrical stimula-

tion, in contrast to the physiological and direct access to the spinal keyboard available through reflex paths; *c*) the more or less indirect nature of the peripheral criteria of this central activity (with its possible remodeling at the level of the spinal keyboard); and finally *d*) the important transformations introduced by the progress of phylogenesis in the organization of these structures which render the results obtained from one species difficult to compare with those from another.

It seems indisputable that the response most easily obtained by applying the stimulating electrodes to the motor cortex is that of a muscular group which is often synergistically activated. The 'physiologically minded' neurologist (128) may then rightly speak of a functional organization of this cortical region. However, proper experimental procedures may reveal the true anatomical arrangement of the cortical motor keyboard. All evidence now available, obtained both by localized stimulation and by destruction, indicates clearly that isolated muscles (22) or even parts of muscles (97) are 'represented' in the precentral gyrus.

The overlapping of the various muscular areas is accentuated when one proceeds from the distal to the proximal parts of the limbs. The localization of the distal muscles of the forelimbs becomes more and more precise when we progress from the cat to the monkey and then to man. The enormous importance assumed by the 'representation' of the hand and of the fingers in man (96) gives us an inkling of the functional significance which must be attributed to this topographical arrangement for the cortical control of discrete movements of the fingers.

Concerning the anatomical basis of this functional representation, it is particularly worth while to search for the architectural transformation which underlies such a phylogenetic advance. The clear individuation in the agranular cortex of man of an area 4γ (area gigantocellularis) penetrating in the depth of the fissure of Rolando, with the identification of the giant pyramidal cells of Betz in the fifth layer, very early attracted attention to this very particular aspect of cortical architecture (122).

These cells increase in number and size, and diminish in density from the anthropoids to man. Numbering 34,000 in the human area 4, according to Lassek (69), they constitute a fine anatomically differentiated keyboard. From the functional point of view, such cells bear direct comparison with the motoneurons of the spinal keyboard. They appear as foci of convergence and of integration for facilitating and inhibiting influences of various origins. They are associated, like the lower motoneurons of the spinal level, with a complex arrangement of internuncial cells which contributes to the modulation of their excitatory state. Thus the patterned activation of the elements of the upper motoneuron keyboard, like that of the spinal structures, depends upon a complex integrative operation.

We now have to specify the paths and the means by which the cortical commands act upon the spinal keyboard.

### *The Corticomotoneural Tract*

The part played by the pyramidal tract in the evolutionary perfecting of the motor system marked it very early as the chief executive pathway by which each cortical motor area controls the musculature of the opposite side of the body. Our knowledge of the pyramidal system, which Bernhard has recently suggested might better be named the 'corticomotoneural tract,' has advanced considerably in the course of the last decade (69). The simplicity of the primitive conceptions has undergone important revisions (see Chapters XXXIII and XXXIV on the pyramidal tract in this *Handbook*).

Particularly, the identification of a group of special fibers in the very interior of this system deserves deeper consideration. It now seems established that the contingent of thick myelinated fibers, which constitute about three per cent of the fibers of the pyramidal tract (69), is formed by the axons arising from the giant pyramidal cells of the precentral gyrus. They, therefore, form the most rapid association path between the motor cortex and the spinal keyboard.

The electrophysiological studies of Lloyd (79) have for the first time precisely described the spinal organization of the pyramidal projections in the cat. In agreement with the histological data of Szentagotai (115), they support the concept of the obligatory relaying of corticospinal messages in the internuncial systems of the spinal cord. The absence of a direct control of the spinal keyboard by the cortical keyboard was at first rather disappointing. It appeared, indeed, to limit greatly the authority of cortical control over the spinal machinery. However, new and precise findings of great importance have been obtained concerning the character of this liaison in the monkey. Thanks to appropriate techniques of stimulation, Bernhard and his collaborators (12) have recently established the existence in the monkey of a

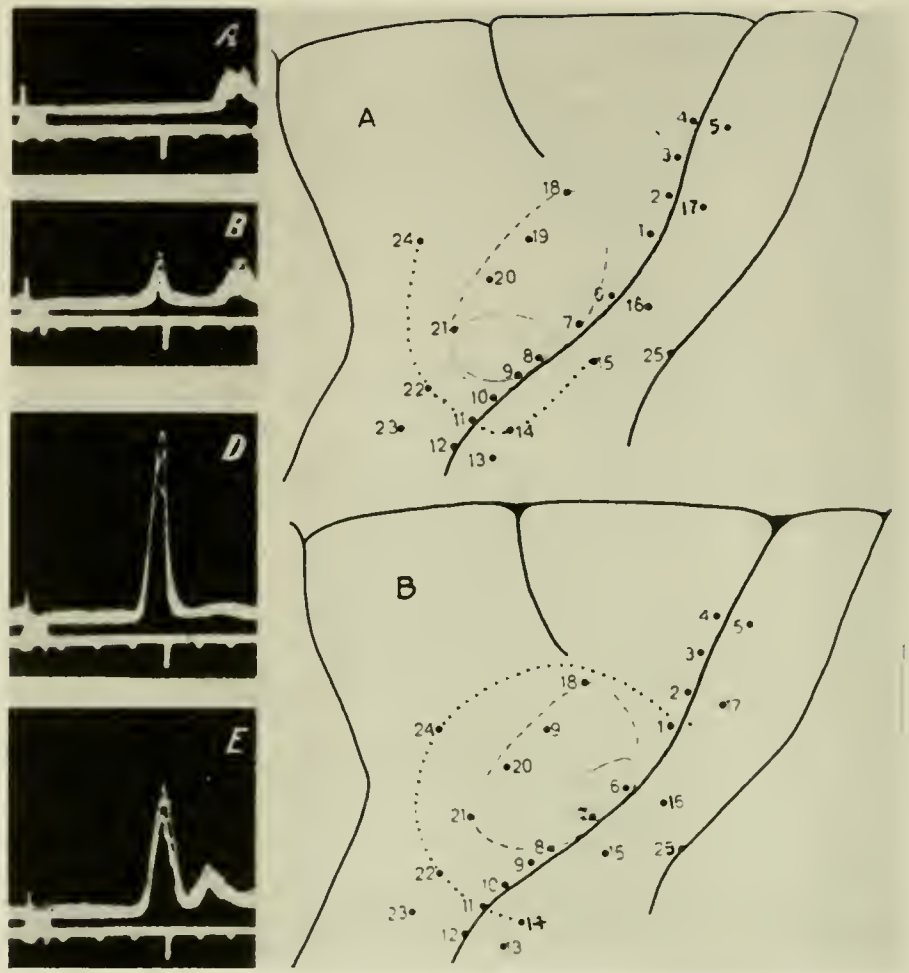



FIG. 5. Electrophysiological investigation of the corticospinal connections in the monkey. *Left:* Superimposed action potentials of the radial nerve following each stimulus in a train of shocks (stimulation frequency, 20 per sec.) delivered to the forelimb subdivision of the right precentral area. The records are obtained at different time intervals after the beginning of the stimulation. *A:* A response of 5.5 msec. latency appears at the beginning of the stimulation period. *B:* After 2 sec. stimulation, a response with a shorter latency (3.5 msec.) is to be noted. *D:* This shortest response becomes maximal after 4 sec. stimulation. *E:* It then disappears progressively after 8 sec. continuous stimulation. [From Bernhard & Bohm (12).] *Right:* Map of the precentral area of the monkey with the position of the 25 different points which were successively stimulated. The responses were recorded in *A* from the contralateral thenar nerve; in *B*, from the contralateral hypothenar nerve. *Circles* drawn in *continuous lines* and in *dashed lines* circumscribe the points which when stimulated give responses of 3 msec. latency and of 5 msec., respectively; *dotted line* indicates the lower border of the 8 msec. 'latency field.' Note that the shorter latency field (direct corticomotoneural connections) for the thenar nerve (in *A*) does not overlap with that for the hypothenar nerve (in *B*). [From Bernhard & Bohm (13).]

direct monosynaptic corticomotoneuronal path. This is in agreement with the histological data of Hoff & Hoff (55). This path uses a selected group of fibers with very rapid conduction rates coming from the cortical keyboard. On the other hand, the cortical region from which the localized responses of short latency can be obtained shows remarkably well-localized muscular sectors (see fig. 5). Particularly significant is the fact that the action of this monosynaptic connection is effective only in the presence

of a prepared background of tonic activity of cortical origin which most probably engages the spinal internuncial mechanism.

These facts have built a firm foundation for concepts, originally expressed by Tower (121), concerning the presumed function of the pyramidal tract.

In the light of the results obtained by cortical stimulation and by localized lesions of the pyramidal bundle in the cat, the monkey, the chimpanzee and man, Tower considers the temporal organization of the pyramidal function to be characterized by two complementary components. One, of tonic nature, is the expression of the excitatory state of the cortical keyboards; it brings a graded contribution to excitation of the spinal segmental mechanisms. The other is a phasic or episodic function superimposed upon the tonic one "which appears as a specific contribution to individual acts of performances and often as the entire performance." This specific action, according to Tower, can be held responsible for the initiation, for the control and for the spatiotemporal patterning of the act. Thus, the fineness of the topographical organization underlies the unique feature of corticospinal function: the ability to bring into action any portion of the skeletal musculature and in all combinations.

Therefore it is tempting, as Bernhard and his collaborators suggest (12), to attribute to the direct corticomotoneuronal connection a privileged role in the control of the fine movements of the extremities. The considerable growth in the number of thick myelinated fibers in the human pyramidal tract makes us expect a still greater development of this system in man. Thanks to this monosynaptic liaison, the motor cortical keyboard therefore directly controls the discharge of the spinal motoneurons. Through the docility of the spinal keyboard, the corticomotoneuronal system which stems from the precentral gyrus can be considered as the chief executor of the skilled movements.

### *The Pyramidal and Extrapyramidal Contribution*

The objective attained by skilled performance is, however, not an achievement of the corticomotoneural system alone. The ability to control skeletal muscle engaged in discrete action directed toward a given end is dependent upon the coordinated action of cooperating muscles and upon complex postural adjustments. The initial activation of prime movers is always accompanied by excitation of synergic muscles and of more proximally lying muscles fixing the joints or sustaining the leading extremity, as well as by graded contraction or relaxation of antagonists. The whole organization of corticospinal relations is then put into play.

To the action of the special contingent of thick myelinated fibers, we must first add the participation of the other components of the pyramidal bundle, including the ones which stem directly from the precentral gyrus. In spite of a considerable number of studies, our knowledge on this point remains imprecise.

The most significant result of localized ablations of area 4 is the definitive loss of the skilled use of the extremities (101, 120, 121). Pribram and his associates speak of a 'scotoma of action' which is produced by precentral resections and which interferes with the skilled use of certain parts of the musculature (101). Such a deficiency may be attributed to the destruction of parts of the motor cortical keyboard. Voluntary control of the musculature is, however, possible by paths other than the pyramidal tract. The consequences of capsular hemiplegias (affecting the pyramidal bundle at the level of the internal capsule) are, as a matter of fact, much more serious than those following lesions confined to the motor cortex. The part played by the pyramidal fibers which stem from other cortical areas (principally the parietal) may account, partly at least, for the severity of such disorders.

On the other hand, all experimental and clinical facts agree in recognizing a route other than the pyramidal path for cortical action upon the segmental mechanism. As Mettler pointed out, "Comparison of the spontaneous and electrically induced behavior of animals after pyramidotomy with the intact animals or with those deprived of all or part of the frontal cortex makes it obvious that the conductive substrate of most of the functions of the frontal cortex is extrapyramidal" (86).

By electrical stimulation of area 4 after section of the pyramids, Tower obtained well-integrated 'synergic movements' and 'significant acts' (120). These movements are poorly localized, however They occur mostly in the proximal part of the members and involve synergistic actions of axial musculature. They are slow in starting and stopping. Hines (51) applied the term 'holokinesis' to this somatomotor activity of a generalized infantile type controlled by extrapyramidal mechanisms (53). This

complex descending system contributes to the excitatory state of the spinal keyboard.

Stereotyped patterned movements integrated at lower levels can be utilized as parts of wholes. Postures can be assumed, modified and shifted so that the instant obedience of a muscle to pyramidal demands could appear. The refinement with which the presence of the pyramidal system supplements holokinesis is referred to by Hines as 'idiokinesis' (51).

Hess (50) described the extrapyramidal function as 'ereismatic' ('ereisma' meaning a framework). It assures the intentional 'telcokinetic' movement (directed to a given end) of its essential frame for economical and precise accomplishment. (This concept is developed in detail in Chapter XXXV by Jung & Hassler in this work.)

Thus, the ability to control skeletal muscle for discrete action is dependent upon the organization of a whole complex motor arrangement. The specificity with which the spinal keyboard responds to the cortical command depends chiefly upon the fineness of organization of the upper motoneuronal keyboard and upon the more or less close connection between the lower motoneuron and the upper one.

It is also significant to note that electrical stimulation of cortical motor areas of unanesthetized monkeys (129) or man (95) never gives forced movements having a dextrous and purposeful gestural allure. The cortical keyboard appears to be only a relay station essential to the execution of fine control of the musculature, but one which receives its activation from other sources. The patterning of commands which is elaborated at its level depends upon superior influences which harmonize the conjoined play of pyramidal and extrapyramidal actions.

## ELABORATIVE ACTIVITY AND INITIATION OF VOLITIONAL COMMANDS

When he tries to probe deeper into the organization of the systems devoted to the elaboration and to the volitional control of the themes of activity, the neurophysiologist quickly appreciates the insufficiency of his present knowledge and the imperfections of his means of investigation. The complexity of the integrative activities put into action at this level seems, at first glance, beyond the reach of the traditional methods of animal experimentation. Normal function seems to be an undissociable complex in which immediate sensorial data and traces of acquired experience are blended with complex psychic elaborations into a dynamic synthesis which is constantly being remodeled. It is toward the clinician and the pathological anatomist that the neurophysiologist now turns in the hope of finding some phenomena accessible to his experimental methods.

### *Data from Pathology*

The clinician gives us a very important clue when he affirms that he can recognize a kind of motor disorder affecting electively the capacity of the patient to move certain parts of the body by intention to attain a given end. This disturbance appears independently of any impairment of the mechanisms for motor execution or of the systems providing sensory information, and of any deficit of intellectual functions. It justifies the concept of a 'praxic' function.

This line of thought becomes still more challenging when it is realized that the accumulated pathological anatomical documents establish the association of certain localized cortical lesions with the disruption of this function. But difficulties soon crop up in the face of the number and the disparity of the various clinical manifestations accompanying such lesions. Further confusion arises from the multiplication of theoretical schemes which have been proposed to provide a coherent explanatory framework into which the observed facts may be introduced. Without entering upon these questions in detail, we shall only consider several aspects useful in our approach to the nervous mechanisms brought into play in the central elaboration of voluntary commands.

Disorders of praxic function can affect separately all kinds of intentional movements. It is important for our study to note that they impair most particularly the acquired forms of skilled manual movements and the activities of the laryngeal apparatus in its relation to speech. Disturbances of the latter historically opened the pathway to the study of praxic functions (17). They are, furthermore, the object of a special field of development (see the chapter by Zangwill on speech in this volume). We shall devote ourselves exclusively therefore to the examination of the former.

According to the initial classification of Liepmann (75) and the many authors who followed him, apraxia represents a disorder of voluntary movement resulting either from a perturbation of psychic planning of action (ideational apraxia), from the

incapacity to mobilize correctly the kinetic formulas in accordance with the established plan (ideokinetic apraxia) or finally from the dissolution of the kinetic formulas themselves (motor apraxia).

In spite of the divergence of views and of the many controversies in which clinicians have been involved concerning the nosologic classification of praxic disorders which, like all classifications, has an artificial character, we shall accept Liepmann's as didactically useful in that it leads us to consider distinctions between different levels of organization in the unitary functional whole involved in praxic functions.

MOTOR APRAXIA. This disability corresponds to the *gliedkinetische Apraxie* of Liepmann (75) or to the *innervatorische Apraxie* of von Kleist (123). Nielsen (90) also speaks of a 'cortical motor pattern apraxia.' It is associated with a more or less specific disruption of the kinetic formulas acquired during the learning of certain specialized movements.

The subject behaves as if he were carrying out, for the first time, these movements which were normally part of his habitual motor repertory. The disorder can take on curious specificities and affect electively special abilities. Such is the case, often reported, of the instrumental amusia which leaves the patient disoriented before his habitual musical instrument, incapable of mobilizing his previously acquired automatisms. Agraphia is another frequently given example in which the patient becomes incapable of directing his pen to form a letter. The same kind of trouble is found in the realm of speech disorders; the buccofacial apraxia which constitutes one of the components of anarthria causes difficulty in the emission of words by a deficit of the corresponding motor patterns.

These disorders are associated with injuries localized in the frontal region immediately adjacent to area 4. Specialized apraxias are accompanied by elective destructions of certain sectors of area 6. Agraphia, for instance, is associated with a lesion of the second frontal convolution, anterior to the precentral gyrus, and instrumental or vocal amusia with a lesion situated in the neighborhood of Broca's convolution (the pars triangularis of the third frontal convolution).

The same cortical regions, as we have seen, also control the complex figures of innate holokinetic mechanisms. Injury to these regions situated more or less largely outside the cortical keyboard is accompanied either by volitional paralysis or by disturbances in the discrete control of the musculature. It causes a specific deficiency in both the innate and acquired kinetic repertories.

These facts, at first sight, seem consistent with the early conceptions formulated to explain the phenomena of memory by postulating the existence of engrams, or traces inscribed in the neuronal arrangements and containing the prefiguration of given patterns of activity.

Without subscribing to the excesses of those who accept the cortical localization of such engrams without qualification, we can however retain belief in the unique role played by these nervous structures, immediately adjacent to the cortical keyboard, in the construction and the organization of given designs of activity. We may note here the homology of this organization with that of the gnosis areas which, on the sensory side, are responsible for the organization of perceptive synthesis. Such mechanisms acquired by experience enrich the primitive repertory of the holokinetic mechanisms; they play an essential role in the orchestration of the idiokinetic melody on the motor cortical keyboard.

Electrical stimulation of these regions effectively produces complex organized movements. Recent experimentation on animals indicates, however, that the results become less striking as we go up the animal scale. Delgado (26) obtained in the cat remarkably integrated purposeful movements in the context of ordinary reactions of the animal. Ward (129) observed in the monkey badly adapted and often undifferentiated motor effects of such stimulation, and Penfield (95) notes in man that no stimulation of the motor cortex is able to activate the engram of organized skilled acts. In the same way, electrical stimulation of the regions for vocalization can only provoke the emission of unarticulated sounds without symbolic significance. (However, the complex structures mediating highly integrated visual and auditory memories are electrically excitable in the temporal regions.)

These findings lead us to think that we must recognize the presence of an intermediary system, capable of organizing the play of the motor cortical keyboard but still receiving its excitation from somewhere else. The study of the second group of apraxias permits us to glimpse something of the nature and the complexity of these excitatory mechanisms.

IDIOKINETIC APRAXIA. This disorder expresses itself by an incapacity on the part of the patient to mobilize the apparatus of action in a manner appropriate to

the goal that he proposes or which is proposed to him. The subject is perfectly aware of the objective to be attained and of the movement to be carried out, but he is impotent in controlling its correct execution. He realizes his error but cannot correct it. He astonishes and irritates himself because of it.

This form of apraxia affects especially the gestures of symbolic character; pointing with the finger in a direction, making the sign of the cross or executing the military salute are generally impossible to execute correctly. In the same way, descriptive gestures, in the absence of the appropriate setting, are particularly disturbed. Generally, as stressed by Lhermitte, the less a gesture offers in the way of pragmatic value, the less directly it is related to instinctive or emotional life, the more it is altered in apraxia (74).

The special feature of this type of apraxia is the fact that the movement which is impaired can be carried out in a perfectly adapted fashion when the patient is under the influence of an emotional experience at a time when it may be incorporated in an involuntary automatism. For instance, he may make the sign of the cross upon entering a sanctuary. The kinetic formulas for the gesture are intact and can still be mobilized in the frame of an automatic reaction. It is therefore essentially the intentional use of these mechanisms which is impaired.

As Alajouanine pointed out, "The disordered gesticulation of apraxics evokes the idea of an involuntary automatism deprived of control" (4). This author insists also on what he calls the syndrome of 'automatico-voluntary dissociation' which approximates the aphasia of Wernike (abolition of the volitional use of language), an aphasia which is therefore a form of idiokinetic apraxia. It must be distinguished from certain aphasias of Broca in which the automatic use also often disappears for certain categories of words only. We can evidently conceive here of an affection of the specific kinetic formulas, as in motor apraxia.

This form of apraxia is encountered usually with a lesion of the cortex predominantly in the region of the second parietal convolution at the extremity of the Sylvian fissure and involving the region of the supramarginalis gyrus.

These observations should lead to the belief that a close relationship exists between the regulation of gestural functions and the data relative to the perception of space both in the body and in the environment.

We owe to Head (46) the first accurate ideas concerning the importance of the integrity of the body scheme for motor behavior. Today, we know that the body represents a frame of reference upon which our knowledge of surrounding space is then constructed. It is in this external space and toward the objects that it contains that we direct our acts. Schilder (106) accurately described the building of the body scheme on the basis of kinesthetic, labyrinthine, tactile and visual impressions. These impressions form, in a constantly remodeled structure embodying the data of the moment with those of past experiences, a dynamic integration which provides our acts and our perceptions with the special frame in which they acquire their significance.

In our ascending search for the origins of the patterning of the motor commands, we are thus led to leave the field of motor integration and to draw progressively nearer the field of sensory integration. We are brought therefore to consider the consequences on motor activity of certain disturbances of perceptive integration. The gnostic and praxic defects are usually so interlaced that some authors like Grunbaum (44) find it difficult to distinguish between them in a generalized disorder. From this standpoint, it should therefore be better to speak of 'apractognosia.' Liepmann already clearly distinguished this category of gnostic deficiency disorders and put them in the category of 'parapraxia by agnosia.'

The relation of certain forms of apraxia to visuognosic disorders has been shown in the 'constructive apraxia' described by Poppelreuter (99). The subject is incapable of constructing symbolic or other kinds of geometrical figures graphically or with the help of concrete objects.

The relation between the disorders of somatognosia is revealed in the 'apraxia for dressing' described by Brain (16). It corresponds, as was shown by Hecaen & Ajuriaguerra (48), to a lesion of the minor hemisphere with hemiasomatognosia.

Finally let us mention the localized disorder associated with a digital agnosia and expressing itself in the complex 'syndrome of Gerstmann.' It is accompanied by acalculia and corresponds to a lesion of the dominant hemisphere (49).

We now appreciate the variety and intricacy of the symptoms of these disorders and the difficulties of interpretation which result therefrom. Perhaps there is reason to reserve a special place for the forms of disturbance which are caused not by a direct impairment of the gnostic areas, but by the rupture of the connections which relate certain tactile, kinesthesic or visual representations to the

psychic processes antecedent to motor behavior. Lhermitte thinks that this rupture is the essential source of the disorganization which underlies the purest and most certain forms of ideokinetic apraxia (73).

IDEATIONAL APRAXIA. The patients who present this disorder are capable of executing upon command simple symbolic gestures but cannot carry out complicated acts which require the harmonious succession of a series of movements. Everything happens as if the patient could not represent to himself exactly, in their proper order, the series of gestures and movements necessary to attain a determined objective—for instance, to take and light a cigarette or to put a letter in an envelope which he must seal. The patient executes correctly each part of the action but mixes them; he commits surprising errors without being conscious of them, for instance he scratches the cigarette against the match box. Certain authors, like Morlaas (88) have, in this case, spoken of an 'agnosia of use.' In this kind of disorder the basic disturbance seems to be connected with a disorder of the conception of the act. The gesture cannot be comprehended according to a coherent preconceived plan. The kinetic figures, although intact, are anarchically mobilized.

It seems very difficult to attribute an accurate localizing value to these disorders which are not very well defined. However, it is important to emphasize the deficiency of integration of the gesture in time which characterizes them. The phenomena described can be related to disorders of temporal seriation or of anticipation observed in animals and in man after lesions localized in the anterior frontal areas (39, 57, 114).

In this connection Dal Bianco (25) introduces the notion of a 'scheme of action' distinct from the body scheme. This scheme implies the unification of action in time: the integration of influences from movements already carried out with the knowledge of those in the course of execution so as to regulate by anticipation the succession of future movements necessary to the pursuit of the action. The essential feature of the scheme of action is therefore its temporal ordination of movements.

We find here again the problem of the nature of the plan of movement that is classically considered as a necessary prerequisite to all volitional activity. It is the *esquisse ideatoire* of the French authors, the *Bewegungsentwurf* of the German authors. It supposes the existence of a so-called motor image or representation of the movement to be accomplished. The early authors assigned an essential role to these residues of past acts which permit prediction of the action in its smallest details and its realization in conformance with the established intent.

Wachholder (124), in his study of voluntary movement, emphasizes the importance of the *Bewegungsentwurf* which contains potentially all the data necessary for the final development of action. Schilder, like Liepmann, has also postulated the presence of a plan of anticipation before any movement. But this plan, according to Schilder (106), is not clearly represented to us. The epicritic components of sensory information play only a secondary role. This plan in its first form should be only the expression of a 'psychic tension' born of the representation of the goal to be attained and energized by the psychoaffective elements of motivation. It is an 'intention directed towards a goal.' The conception of the proper means to attain this goal is hardly conscious. The early stage of the plan will develop and take form through a process of dynamic construction in which the 'postural model' necessary for the act is organized in the frame of the usual representation and the actual image of the body. The visual elements generally play a determining role in the appreciation of the spatial relations which precede intentional action. Then, as soon as the movement is started, the movement is performed thanks to the sensory data born of the action itself. It proceeds until the projected objective is achieved under the influence of the successive structurings of the plan of action.

Psychologists have underlined the important place held by the affective element, the desire or tendency which favors the structuring of the intention, motivates the incitation of the act and sustains the realization until the final goal is achieved. The recognition of particular disorders of motor initiative, the *Antrieb* of the German authors, emphasizes the role which must be reserved to these basic motivational factors in the starting and in the dynamic sustaining of the action. We agree in acknowledging today the part in these manifestations which the rhinencephalic structures play in strict liaison with the anterior frontal regions of the cortex (39, 84, 100). They are integrated with the most general mechanisms controlling vigilance which are resident in the reticular formations of the brain stem (27, 76, 81).

Finally, the study of the problem of apraxias has brought up the question of cerebral dominance. The inequality of use and especially of skill of the two hands is well known in man where we generally

find a predominance of the right hand associated with a dominance of the left hemisphere. It is known that no clear differences in the organization of the cerebral cortex have been found between the two hemispheres. The coexistence of speech disorders with lesions of the left hemisphere should draw attention to this problem. The study of the apraxias reveals, on the whole, the dominating control exerted by one of these hemispheres, the so-called 'major hemisphere,' upon the other. The lesions of the 'minor hemisphere' cause disorders of unilateral character which are more easily compensated than the bilateral ones following a lesion of the major hemisphere.

The origin of this dominance is still controversial. The suggestion that inequality of vascularization might cause an asymmetry in the development of the two hemispheres was once advanced by anatomists. It can no longer be sustained today. As observed by Tournay (117), the maturation of the left side may be more advanced than the right side in the future right-handed child. The role of learning seems, however, to be predominant, as shown by the remarkable compensation observed to follow hemispherectomy in young subjects (62, 126).

### *Neurophysiological Data*

Confronted with the complexity and the difficulty of the problems brought up by the clinicians, the neurophysiologist appeared rather helpless, until recently. However, the ever increasing improvements in his experimental techniques have now given him new means of progress. Indeed it is to the recent development of electrophysiological methods of exploration of cortical activities in man and to the technical ability of brain surgeons that we owe the opening of a new chapter in the physiology of voluntary action. Thus, the great neurosurgeon Penfield does not hesitate to claim: "There is enough evidence available from the study of the human brain for consideration of the problem of voluntary movement on a physiological basis," and he invites the neurologist to examine objectively the new evidence "without the bias from current clinical teaching."

It is now beyond doubt that the idiokinetic patterns of activity which animate the cortical motor keyboard do not depend upon the origination of nerve impulses in the cortical motor area itself. The 'motor power of its activities' comes from somewhere else. Therefore the motor cortex appears as a funnel of convergence for the stream of patterned impulses which produce voluntary movements. The disorders of the praxic function allow us to glimpse the complexity of the mechanisms implicated in this canalization of the stream of sensory afferent influences to the core of the integrative structure where the planning of the act takes place. A series of questions thus present themselves to the neurophysiologist. What are the nervous structures implicated in the successive stages of this transformation? By what paths are the transmission and the transformation of the sensory patterns carried through the associated structures to the integrative structure where the messages which will animate the cortical instrument of motor commands are elaborated? What are the nervous mechanisms which make possible this selective patterning of excitation within the neuronal sets of the cortex?

CORTICAL PARTICIPATION IN THE ELABORATION OF VOLUNTARY MOVEMENT. It has become classic to localize the most complex integrative elaborations in the core of the neocortical nervous structures. The long controversy which, until the modern period, divided the believers in a functional globalism from the partisans of the specific activity of anatomically localized structures is likewise traditional. To admit that the brain functions as an indissociable whole must not prevent us from trying to determine the nature and to analyze the mechanisms of its functional cohesion. Thus, the pathological anatomy of praxic disorders cannot but bring us several important orienting facts concerning the particular role of certain associative areas of the cerebral cortex in the elaboration of the components which cooperate in the patterning of voluntary commands, more particularly the parietal areas with the neighboring gnosic regions, the frontal areas and especially the regions anterior to the principal motor area.

Now, where in these structures can we place the higher level to which Jackson attributed the supreme power of unifying synthesis? At first sight, no available argument permits us to assign to it a precise localization in the core of the neocortical structures. To propose that this integrative operation results from the complex interplay between the diverse functional areas of the cortex thus offers an acceptable hypothesis. Histological and neuronographic methods have revealed the richness of the connections which tie the various sectors of a cortical hemisphere together and the importance of the liaisons which associate them by callosal paths with the homologous regions of the opposite hemisphere. Our present knowledge of the fine myelo- and cytoarchitectonic organization of the cortical structures is still too imprecise to permit us

other than speculative interpretations of their mechanisms of functioning.

A series of experimental arguments are, however, available which seem to minimize greatly the functional importance of these connections between the various cortical areas for the integrative operations. Since 1924 Lashley (68) has emphasized the unexpected fact that incisions distributed through the cortex of a cat, in all possible vertical planes, made in such a way as to disrupt the interareal connections, are without marked consequences on the comportment of the animal and on its capacity for retention.

Sperry (111), followed by Wade (125), made analogous findings in monkeys by isolating the motor cortex from the neighboring areas, a procedure not producing notable perturbations in the motor behavior of these animals. In man, Akelaitis (3) has shown that section of interhemispheric transcallosal connections is without influence upon motor functions. Agenesis of the corpus callosum is also without apparent motor effect (32, 62). Finally, Penfield (93) has shown that a nearly complete isolation of the precentral gyrus from the neighboring areas leaves intact the capacity of the individual to execute skilled acts. No functional participation of the U-shaped sensorimotor connections has been observed (95). Thus, in the interior of the motor area the neighboring regions seem to be connected vertically by means of subcortical circuits.

In view of the astonishing resistance of the cortical elaborative functions to such mutilations, it becomes manifestly difficult to attribute to the horizontal intracortical paths a functional role of the first order. Penfield concludes, "Transcortical connection must serve some useful function but, in all events, this function is not essential for voluntary action" (94).

The precentral regions are, therefore, under the direct control of certain subcortical structures. The stream of impulses that produces the patterning of skilled activities at the level of the precentral gyrus most probably comes from such subcortical regions. Thus it seems logical to search for some kind of centralizing structure in regions which are in functional connection with the different sensory and associative sectors of the two hemispheres.

CONCEPT OF A CENTRENCEPHALIC SYSTEM OF INTEGRATION. Penfield has introduced the concept of a subcortical system of integrative coordination which he designates 'centrencephalic' (93, 95). Without assigning to this essentially functional system a precise anatomical location, Penfield places it in the highest level of the brain stem, as Herrick defined it in 1880. It comprises a group of mesencephalic and diencephalic structures (including the thalamus) which have direct functional connections with the two cerebral hemispheres.

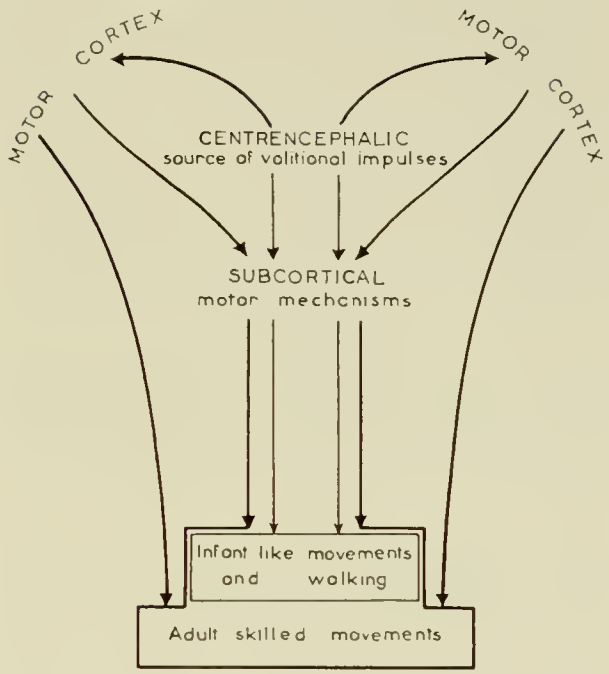



FIG. 6. Hypothetical diagram of the stream of volitional nerve impulses producing adult skilled movements (in *heavy lines*). The impulses come from the centrencephalic area to each Rolandic motor cortex and from there descend to subcortical motor mechanisms and peripheral bulbospinal motoneurons. In *fine lines* are shown the course of nerve impulses producing voluntary action without involvement of the motor cortex. [Modified from Penfield (94).]

The importance of such a region is revealed by a series of clinical (93) and experimental findings (58, 82, 95). They agree in establishing the anatomical identification of the complex fields of reciprocal relations which unite the specific and associated portions of the thalamus, as well as the diffuse systems, with the different sectors of the cortex.

In the series of nervous events which underlie the preparation for and the initiation of a voluntary movement, Penfield emphasizes the special features of this transactional operation which suggest that it is responsible for the emission of 'voluntary' commands (see fig. 6). This 'final integration' must be assigned, according to him, to the centrencephalic system. "Only with a centrencephalic system of this sort

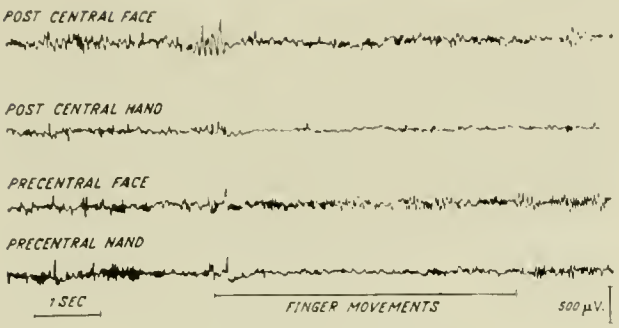



FIG. 7. Electrocorticogram recorded in the Rolandic region in man. Note the beta rhythm (25 per sec.) from the precentral areas. On command to move fingers, the resting rhythm disappears in the hand area, but not elsewhere. It reappears when movement stops. [From Jasper & Penfield (59).]

could a stream of willed impulses be initiated, capable of producing the action that is appropriate to all previously received information" (94).

Two experimental findings, drawn from the study of the electrical activity of the cortex, have been put forward in support of the hypothesis of a subcortical origin of voluntary commands. The first is the identification of a type of electrical activity, specific to the precentral regions, which appears in the electrocorticogram as a regular rapid rhythm of 25 per sec. and an intensity of 100 to 250 mv. It can, under favorable conditions, be detected even in the encephalogram where it often takes the form of an arch-shaped rhythm of 12 to 13 cps which Gastaut (40) identified as a 'dedoublée' form of the basic beta rhythm. Such rhythmic activity, as well as the other forms of alpha activity, is generally associated with a state of relative functional rest in an awake subject.

Furthermore, just as the alpha rhythm of the occipital areas, for example, appears blocked by visual stimulation and indicates a state of functional 'activation' of the perceptual system, a blocking of the rolandic beta rhythm appears when a voluntary movement is being initiated and persists during its execution. Jasper & Penfield (59) emphasize the localizing value of this blocking on the precentral areas. A movement of the fingers, for instance, blocks the rhythm of the precentral regions relative to the hand while allowing the rhythmic activity of the neighboring regions to continue (see fig. 7). These facts have been confirmed by others, in particular by Gastaut (40, 41) in relation to arch-shaped rhythms. Penfield & Jasper emphasize another particular aspect of this phenomenon; the blocking of the rhythm seems to be associated directly with the kinetic component of the intentional movement. It occurs, for instance, if we ask the subject to execute a series of movements such as displacing the thumb successively with the different fingers. In contrast, the active maintenance of a posture is marked by the rapid reappearance of the basal activity (59).

Penfield & Jasper accordingly suggested that the impulses responsible for this abolition of the resting rhythm may have a subcortical origin. As a matter of fact, the evidence now accumulated by neurophysiologists confirms the role of the subcortical centrencephalic systems in the regulation of rhythmic electrical activity of the cortex (63, 95). The origin of the afferents responsible for blocking and its time relationship with the beginning of the movement remain however to be made more precise.

A second group of experimental facts concerns another group of correlations recently established between motor behavior and electroencephalographic data. The existence of a significant relation between the very first signs of muscular activity and the phase of the alpha rhythm of the rolandic regions, during the initiation of a voluntary movement, comes from the experiments independently carried out by Boreham *et al.* (14) and by Bates (8). Lansing (64), studying the reaction time, found it to be shortest when the stimulus and the response both fall in the same phase of the alpha rhythm recorded from the occipital and rolandic areas. [See also Lindsley (77).]

The interpretation of these data remains difficult. However, it permits us to envisage a relationship between the mechanisms of origination of voluntary movement and those which control the cortical rhythms.

The earlier hypotheses of Bartley & Bishop (7) concerning the existence of a relation between the cortical alpha rhythm and the fluctuations of the excitability of the cortical neurons, as well as the observations of Adrian & Morruzzi (2) on pyramidal discharges attending the slow waves recorded at the surface of the cortex, may locate the seat of this interaction at the cortical level. On the other hand, the role of the subcortical structures located in the centrencephalic areas of Penfield in the control of the basic rhythms of cortical activity could also justify the hypothesis that the interaction is located at the supposedly subcortical source of the messages which evoke voluntary movements.

It would be unjustified to overemphasize the value of such experimental evidence the interpretation of which still remains quite hypothetical. In any event, Penfield's very interesting views on the centrence-

phalic source of volitional impulses must not lead us to underestimate the certainly important role of the neocortical structures in the process of elaboration and initiation of voluntary movement.

The fundamental problem, set by the nature of the neurophysiological basis of the conscious decision which finally liberates the patterned stream of nerve impulses, remains untouched however. As Penfield further emphasizes: "These questions impress themselves upon us for an answer. They bring clinical physiologists face to face with psychologists and the religious philosophers in what may be called a common perplexity" (94).

MECHANISMS OF PATTERNING AT THE NEURONAL LEVEL. The problem of the mechanisms implicated in the patterning of central nervous activities clearly remains unsolved. This field, hardly accessible to direct experimental study, is open to theoretical speculations inspired by various considerations (29, 61, 67, 92, 98, 130). With wisdom, Lashley (68) thinks that "the law of parsimony requires that every effort be made to explain all integration in terms of the demonstrated modes of interaction of nerve cells before some different and unknown process is postulated."

Most of the hypotheses which are based upon the functional dynamics of synaptic or ephaptic interactions strive to designate the part played in the patterning of nervous activity by the structural arrangement of the neurons into appropriate patterns of interconnections.

The study of nervous architectonics reveals a great variety of organizations of the polyneuronic structures. To the well-ordered grouping of the long specific afferent and efferent paths in the nervous organization may be contrasted the apparently random distribution of the short neurons in the network of the brain stem and of the associative sectors of the cortex. The former is particularly suited to the faithful transmission of the spatiotemporal feature of an organized nervous message. But difficulty arises as soon as we try to follow the destiny of these patterns and their remodelling in the stochastic network where, everybody agrees, the most complex integrative operations are located (34).

"There are some thousand million neurons in the human cerebral cortex and each is a node in the network whose strands are woven from the numerous processes (dendrites and axons) that provide the multiple synaptic contacts. Each node would be the converging point of scores of paths and each in turn would project to scores of other nodes" (29).

Many authors have speculated on the exceptional functional properties that such an arrangement could confer on the nervous structures which possess it. Various theories have been proposed to explain the functioning of these networks (21, 34, 68, 102).

The anatomical complexity of the interneuronic connections and the great capacity of these ensembles to compensate after experimental destruction led to the conception of a kind of functional undifferentiation (equipotentiality). The mere numerical consideration of the available cells in relation to the different patterns of excitation possible leads us also to exclude, at first glance, the hypothesis concerning the existence of a specialized circuit for each configuration of activity. In fact, each neuron of the network can be engaged in various patterns of activation. The pluridimensional network thus offers an infinity of possible configurations with a limited number of elements (29).

Eccles, for his part (29), postulated the existence in the interneuronic arrangements of the network of a given structural specificity, inherited or acquired and open to remodelling. It would sensitize given circuits to given modes of activation defined in the afferent sectors of the system and would canalize these actions electively through the activating structures of efferent systems. The shunting of these circuits of activity could also be submitted to the modulating actions of a peculiar type. In this connection, Eccles tries to confront on a neurophysiological plane the problem of the modulating influences of the 'will.' "There can be no doubt that a great part of the skilled activity evolving from the cerebral cortex is stereotyped and automatic. But it is contended that it is possible voluntarily to assume control of such action" (29).

To give an account of such control, Eccles is led to postulate the existence of a 'field of influence' capable of modifying the intrinsic spatiotemporal activity of the neuronal network. The quantitative aspect of the spread of activity in neuronal networks and the physical implications of such a mechanism are taken into consideration and lead Eccles to suppose a so-called 'detector function' proper to these neuronal networks which he makes the basis of the essential operations of the 'matter-mind traffic' (29).

In this field we can, with Eccles, conceive the pattern of volitional impulses emerging from the integrative network as being determined by three factors: *a*) the afferent input and its spatiotemporal characteristics; *b*) the microstructure of the neural

nct and its specificity of organization (inherited or acquired); and *c)* the postulated 'field of extraneous influence' exerted by 'will' or 'mind' capable of controlling, orienting and modifying the stream of influence converging toward the effector structures of the system.

Such formulations, as stressed by their author, only push back the difficulty of solving a problem which remains posed in all its hermetic complexity—how to conceive, indeed, the nature, the origin and the maintenance of such a 'field of influence,' the action of which is so powerful and the spatiotemporal organization of which appears as an ineluctable necessity which is still to be explained.

Endeavors are numerous in this field but, as Sperry so well stated it, "it is not a solution we aspire to, but only a basis on which to begin" (113). Unless the scientist can soon have at his disposal a new technique suitable for attacking such problems experimentally, the 'enchanted loom' as poetically imagined by Sherrington (107), weaving its "shifting harmony of dissolving but always meaningful patterns," will long keep its secret.

## ADAPTIVE PLASTICITY OF THE SYSTEM OF ACTION; ITS CONDITIONS AND ITS LIMITS

The formerly classic concept of a motor projection containing all the detailed elements of the patterning of command, like the perforated music rolls of a mechanical piano, now appears clearly untenable. It would necessitate on the part of originating structures and mnemonic functions a gigantic task very difficult to conceive in terms of nervous mechanisms. The most perfect pre-existing plan could not account for the astonishing capacity of the nervous system to adjust our movements to the ever-changing and most unforeseen circumstances of their achievement.

The aphorism of Claude Bernard, "We will, then a function is achieved on its own," is more in accordance with our intuitive apprehension of the reality of such phenomena with all that they imply concerning prestructured arrangements and automatically achieved regulations. The structures originating voluntary movement intervene to foresee, to start off, to direct and to stop the working of complex machinery which contains in itself the regulating elements of its own activity.

It must be borne in mind that the fundamental framework of this machinery is made up of an assembly of neurons anatomically ordered into appropriate patterns of interconnections. Among these elaborate and intricate patterns of synaptic linkages, some are preformed and organized directly in the growth process itself, others are adjusted by functional regulation through learning processes (112). Both constitute a kind of 'motor repertoire' upon which the animal must draw for most of its performances.

The extent to which and the means by which such basic neuronal architecture provides the structural basis for the plasticity of its functional effectiveness must now be considered. In approaching the problem of plasticity it appears useful to distinguish, with Weiss (130), two quite different aspects of its expression in behavior.

On the one hand, we may consider the range of adaptability which in some degree characterizes all, even the most stereotyped, modes of motor performance. As a rule they present, within given limits, some degree of variability in their formulation by central commands and in their adjustment to environmental changes. Plasticity is thus understood as "elasticity within a given qualitative performance admitting of quantitative adaptation to what, for the given species, is a normal range of variability of the environment" (130). We shall refer to this first aspect as the flexibility of the usual or inborn forms of action.

On the other hand, we must take into account a faculty of the organism to adapt its motor comportment to new situations by inventing novel coordinating patterns and in fixing them in the structure. It adds new elements to its own motor repertoire. Plasticity is defined there as the "ability of an organism to cope with emergency situations lying beyond the normal range of elasticity, by creating new performances previously not even latently in existence" (130). This second aspect is to be referred to as the adaptative learning of new forms of action. Let us examine first the conditions and the limits of the 'flexibility' of motor performances.

### *Flexibility of Motor Performances*

To adapt performance in accordance with external changes requires that the motor centers be, somehow or other, informed of these changes. Therefore, we are immediately faced with the problem of sensory control of the adjustment of motor performance.

REGULATIVE ROLE OF SENSORY INFORMATION. Since Charles Bell (10) recognized the fact that motor action is impaired by breaking the 'circle of nerves' which conveys the command from the brain to the muscle

and sensory messages back from the muscle to the brain, the part played by sensory control in the coordinating of movement has been clearly recognized. Claude Bernard stressed the regulatory role of sensibility in "giving the signal which moderates or which accelerates" (11), and Exner (31) enunciated his principle of 'sensomotility' which asserted the unitary whole of sensory-motor functions. Furthermore, it seems unnecessary to recall the emphasis laid on the afferent input in all reflexological theories of motor coordination.

Observation of motor defects following sensory disturbances in mammals, as well as clinical observations in man, has confirmed the outstanding importance of sensory information in regulating motor performance. The crude performance of ataxic patients, as well as the motor impairment of deafferented animals, emphasizes the extent to which the normal functions are impaired when the centers are prevented from receiving muscular sensory messages. Precision is lacking and adjustment remains crude, although in man functional capacity may be later partially restored with the vicarious aid of vision.

The importance of sensory messages coming back from the periphery for the initiation and the control of the movement is especially well illustrated by the early observations of Mott & Sherrington (89) in a monkey having partially or completely deafferented forelimbs. The monkey appears to be reluctant to make voluntary use of its completely deafferented arm. The whole motor mechanism is however intact and can be activated quite normally in primitive defensive or attacking acts under emotional stress; but in the normal course of life, there is no attempt by the animal to use such capacities in an intentional manner. Thus, the elimination of sensory innervation produces a kind of localized apraxia. It is noteworthy that the preservation of small parts of the cutaneous innervation of the member appears to be sufficient to preserve the effective use of the otherwise deafferented limb (89).

Furthermore, experimental analysis has given us important information concerning the functional organization of the complex spinal machinery. The excitatory state of the spinal keyboard, which ultimately conditions its reactivity to cortical commands, appears to be finely modulated by a great variety of regulatory influences of reflex origin. We know, for instance, the contribution of stretch reflexes to the smoothness of muscular contraction, and the participation of proprioceptive messages in the complex postural adjustments of the body musculature (see Chapter XLI by Eldred on posture in this *Handbook*).

Although less complete than the preceding, our present knowledge of the functioning of the cortical motor areas also indicates clearly the modulating action of sensory origin which conditions the excitatory state of the upper motor neuron keyboard (15). Of particular interest for our purpose is the role of the neocerebellum which seems to be directly involved in the mechanism of control of the discharge of corticospinal impulses (2, 127).

The neocerebellar cortex which in man and, to a lesser degree, in the other higher primates surpasses the more primitive cerebellar structures in size and functional importance assumes an important part in coordinating voluntary movements. Injury to this mechanism causes, among other effects, very characteristic disorders in the spatiotemporal patterning of the voluntary command. The weakness and the lack of precision of the movement, the poor timing of its components (asynergy), and the forced oscillations of the limbs at the start and at the end of the movement (intention and terminal tremor) are common features of neocerebellar disorders which are manifested in a variety of ways (56).

Even at the levels at which volitional impulses originate, the modulating action of sensory messages at every moment keeps the activity of central structures in harmony with the varying position of the body parts in movement and with the state of the ever-changing external field of action.

Still more broadly, we may consider the total afferent influx as producing, by way of both its specific and unspecific channels of distribution throughout the central structures, a continuously shifting background of central excitability. We have already been led to consider the part of such dynamogenic influence in the arousal of motivational forces which put to work and which sustain the voluntary control of action.

Therefore the spatial and temporal pattern of impulses required for a purposeful movement cannot be seen as automatically and blindly released into the channel of the executive pathways by the originating structure. It is progressively built up by the spread of central commands through the lower structures. It is remodeled at each way station of the executive system in accordance with the modulating influences which converge from the peripheral sensory mechanisms.

All these facts emphasize clearly the outstanding role played by the regulative action of sensory origin

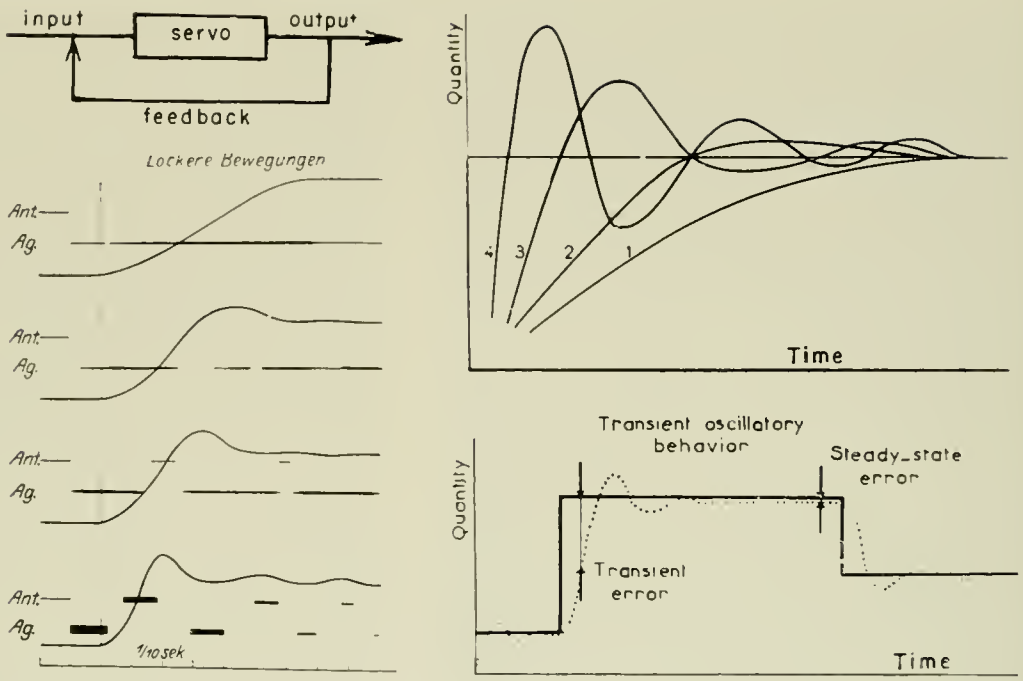



FIG. 8. *Upper left:* Schema showing the principle of organization of a servomechanism unit. *Lower left:* Distribution of the muscular activity in two antagonistic groups of muscles, the agonists (*Ag.*) and antagonists (*Ant.*), at four stages of increasing speed of movement. The electromyographic activity of each group is schematized by a *line* the thickness of which varies with intensity. The *mechanographic record* shows the increasing tendency to oscillation when the speed of execution is increasing. The final position is achieved only by a transient oscillatory movement. [From Wachholder (124).] *Upper right:* Diagram showing transient stability of a physical system with varying degrees of damping. *Curves 2, 3* and *4* are progressively underdamped and show increasing degrees of oscillatory behavior. *Curve 1* is overdamped and shows great stability at the expense of a long response time. A servomechanism shows a similar mode of functioning. Compare these curves with those recorded by Wachholder. [From Brown & Campbell (19).] *Lower right:* Response of a human subject in a tracking experiment. The diagram illustrates the several kinds of observed errors between the response (*dashed line*) and the command (*solid line*) during a sudden change in the latter. A steady state and transient errors, as well as transient oscillatory behavior, are also characteristic of the performance of a servomechanism. [From Ruch (103).]

at each level of the nervous organization. We now have to search more precisely for the principle of organization of such a regulative action which automatically leads the prearranged motor performance to its correct achievement.

MECHANISMS OF SELF-ADJUSTMENT. As a matter of fact, the recent new developments in control systems and communications provide attractive analogies and promising suggestions for a better understanding of this problem (19, 36, 54, 133). For biologists, the most interesting control systems are those commonly called 'servomechanisms' or slave systems. Components and characteristics of servomechanisms are numerous and varied, but their common feature is that they possess some kind of controlling device able to appreciate continuously the discrepancy between the state of the machine realized at a given moment and the final aim assigned to it by its constructor. Through a 'feed-back' circuit, the information collected from an error-detecting device is at every moment sent back to the servomotor controlling the output. By modifying the input command it permits the output to be corrected for the detected discrepancy. Thus the 'behavior' of a servomechanism is not governed by a blind obediance to the order of a predetermined program of action, but it presents a kind of self-adjustment by modifying the input command of the system as a function of its output.

Such 'teleological' mechanisms (36) are designed

to attain a given goal (such as attainment of maintenance of a given equilibrium or pursuit of a moving goal) by their operation despite unexpected changes occurring (within a certain range) in the field of external forces. They present a type of 'flexibility' of their performance. They give a clue to understanding how a simple physical system, the organization of which rests on unmodified rigidly connected working parts, can, thanks to the feed-back action, present a certain range of freedom in the adjustment of its performance. Homeostatic processes and more general neural activities have been analyzed in this way (54, 83).

Attempts also have been made to approach certain aspects of human sensorimotor behavior in the same way. Although too schematic and too simple to account for the complex total process involved in human behavior, the analogies with the physical systems just described provide a suggestive model for the dynamic aspects of human controller tasks (23, 24). Figure 8 shows some aspects of these analogies.

The analogies between the mechanisms of voluntary movements and those of servomechanism are also found to be close, although not complete (103). The stream of volitional impulses which initiates skilled movements may be seen as a programmed input which puts to work the cortical motor mechanisms considered as part of a complex servomechanism.

Several closed loops have been identified which modulate by feed-back control the emission of corticofugal impulses. Some are long loops including either various proprioceptive or exteroceptive feed-back circuits, more or less directly coupled with the organ of movement or with the outcomes of the action; they constitute, therefore, 'output-informed' feed-back circuits. Others are shorter loops connecting the motor cortex to the cerebellum or to the other subcortical way stations. They do not include the peripheral output of the system, and hence constitute what Ruch calls 'input-informed' circuits (103). Organized close-loop controls have been found at all levels of the nervous system (see fig. 9).

The spinal machinery presents the closest comparison with the servomechanisms (85). Thanks to its many self-regulating circuits, it gives to its output, the contraction of muscle, smoothness and precision. Despite the classic view of reflexes as stereotyped reactions of a rigid prearranged apparatus, this reflex machinery taken as a functional whole appears as a self-adjusting mechanism of high flexibility. Such systems adapted to local regulations are included in larger functional units likewise organized as self-regulatory devices of a higher order of complexity. We know, for instance, the astonishing flexibility of postural regulatory systems. Taken as a whole, such systems act like time-continuous error-detecting devices that position the body in space by varying the output of the muscle to counteract changes in gravitational force (103).

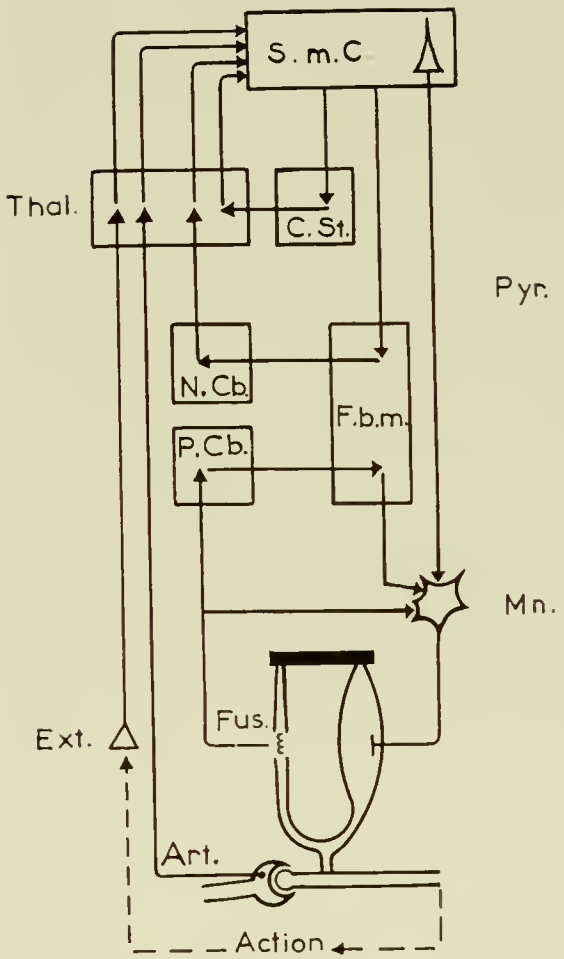



FIG. 9. Simplified diagram showing some examples of output- and input-informed circuits playing part in the control of motor command. *S.m.C.*, sensory-motor cortex; *Thal.*, thalamus; *C. St.*, corpus striatum; *Pyr.*, pyramidal tract; *N. Cb.*, neocerebellum; *P. Cb.*, paleocerebellum; *F.b.m.*, bulbomesencephalic formations; *Mn.*, motoneuron; *Fus.*, intrafusal receptors; *Art.*, articular receptors; and *Ext.*, exteroceptive receptors.

According to Ruch (103), the corticocerebellocortical circuit may also represent a part of a mechanism by which an instantaneous order of cortical origin may be "amplified and extended forward in time." It should be efficient in starting and in stopping

a movement without jerkiness. This might be accomplished by a controlling feedback proportional to the velocity of the movement. In this view "cerebellar tremor may be comparable to the oscillation of an undamped servomechanism in which the feedback is removed."

Ruch likens the cerebellum to the 'comparator' of a servomechanism which receives from the cerebral cortex some representation of the command, and from the muscle and other exteroceptors a representation of the resulting movement. These, compared, may result in a signal which when transmitted to the motor cortex alters its commands to the muscles so as to diminish the discrepancy.

The higher integrative levels themselves, which operate within a system of higher order, do not escape the same basic mode of organization. Thus, the whole nervous system will have to be viewed as a functional hierarchy of systems, each of which includes subsystems and so on, a view already stressed earlier by Weiss (130). At all levels of this hierarchy, we shall find the same common principle of organization of sensorimotor functional units.

A principle of circular regulation seems to govern the fundamental mode of relation which ties the efferent to the afferent portions of the nervous system either inside the body or through the external medium. Thanks to its self-regulating mechanism, each working unit of this system assumes, in a given range of flexibility, its own functional balance in accordance with the requirements of the general equilibrium which results in this internal unit contributing to the effectiveness of the organism as a whole.

We are then led to the older concept of 'sensomotility' of Exner, as well as to its more recent expressions (43), to conceive the dynamic patterning of nervous commands as a result of the continuous stream of nerve impulses which is carried along a variety of circular paths that form closed loops at various levels of an anatomically ordered structure and which flows continuously from sensory receptors to effector organs, as shown in figure 10.

Space does not permit further discussion of the several functional implications and the necessary limitations of such a principle of organization in its theoretical as well as practical aspects. Although we may speculate concerning its broader significance

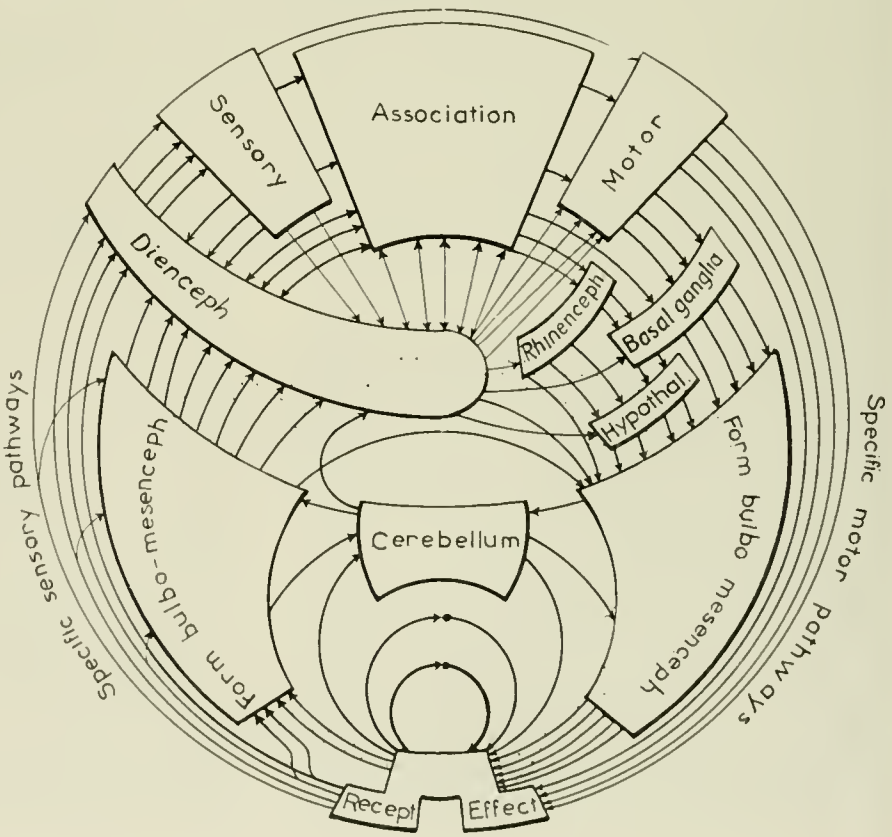



FIG. 10. Highly simplified diagram of the chief sensory, associative and motor paths throughout the nervous system, which illustrates the circular organization of the sensorimotor relations at any levels. Only the 'output-informed' circuits are represented. Some direct sensory connections to various higher structures have been intentionally omitted.

for the analysis of living organisms as teleological systems of action (36), we will assert for our restricted field its undeniable explicatory power to account for the flexibility of motor performance which, in other respects, is dependent on a prearranged pattern of neuronal interconnections.

We are now faced with our second problem. How can we conceive the mechanism by which the organism may improve upon its own structure and may invent new forms of action?

### *The Acquisition of Motor Skills and the Learning Process*[1]

A basic fact must be kept in mind when trying to approach the problem of the neural basis of motor learning, namely that the muscular keyboard does not immediately allow all possible chords. The central commands are bound to operate upon it through the pre-existing arrangements of its inherited or most usual modes of action.

Therefore, as also emphasized by the psychologists concerned with learning, to learn a new act does not consist in creating out of nothing a new motor pattern by putting together in proper sequences the anatomical units of the motor machinery. Learning requires, before anything else, a disrupting of some pre-existing functional units (45), then a selective choice of the useful motor combinations, and finally their assembling into a new working unit.

For convenience of analysis, it will be of some interest to distinguish two complementary aspects, both intimately involved in the learning of a new act. The first is more especially related to the initial phase of learning; it concerns the activity required of the higher control to tide over the difficulties encountered and to achieve the proposed end; it implies a selective operation. The second is related to the learning process itself and finds its final expression in the automatically achieved act which becomes almost completely independent of higher control; it implies the stabilization of the fixation of a new pattern of nervous activity.

ACHIEVEMENT OF A NEW PURPOSEFUL ACT. Perfect as the self-regulatory mechanisms may be, they are incapable of executing immediately with the required accuracy a purposeful act having an aim which is beyond the limit of flexibility of the individual's motor repertoire.

The mastering of the basic movements in the first years of childhood and later of the skilled movements or technical abilities is accomplished, first of all, through a process of fumbling and progressive adjustment. Psychologists have defined the essential characters of this progress. The initial phase involves a first inventory of the means to be put into action to attain the proposed goal. From the very outset, the most important part seems to be played by regulatory perception. The improvement in motor performance is essentially characterized by the selective restriction to movements strictly necessary to make the action effective. Psychologists also insist on the importance of the perceptive organization from which the elaboration of the 'motor image' or representation of the act proceeds. A significant part is played in this by the model of the act existing in the subject's central nervous system (45). The achievement of a new act therefore depends upon a complex modulator operation which involves the higher level of integration.

The main concern for our understanding of the neural mechanism involved is that this selective and adjustive capacity of the higher levels is limited in setting up new patterns of action by its power to remodel or abolish the existing ones. Therefore, the limits of the learning process proper appear to be determined by the extent to which the functional units which produce internal remodelings of higher origin can operate. The nature and the importance of these functional units vary with the species and in a given species with the different parts of the body, discrimination being more accurate in the forelimb than in the hind limb, and in the distal part of the limb than in the proximal.

Such facts obviously suggest that motor learning capacities should be closely related to the degree of refinement in the connections between the higher and lower levels of motor arrangements. Such a statement seems fully justified by the data available from the results of experimental as well as therapeutic nerve regeneration or muscle transposition. These operations, which impair the effective performance of a given muscular group, are of interest in imposing on the learning capacities of higher levels the necessity of remodeling inborn primitive patterns of coordination in order to re-establish the adaptive use of a limb.

As shown by the now classic experiment of Sperry (110), a rat fails to re-establish a correct functional adjustment of the action of antagonistic muscles when their tendinous attachments have been reversed. As

[1] This topic is the subject of Chapter LXI by Galambos and Morgan in this *Handbook*.

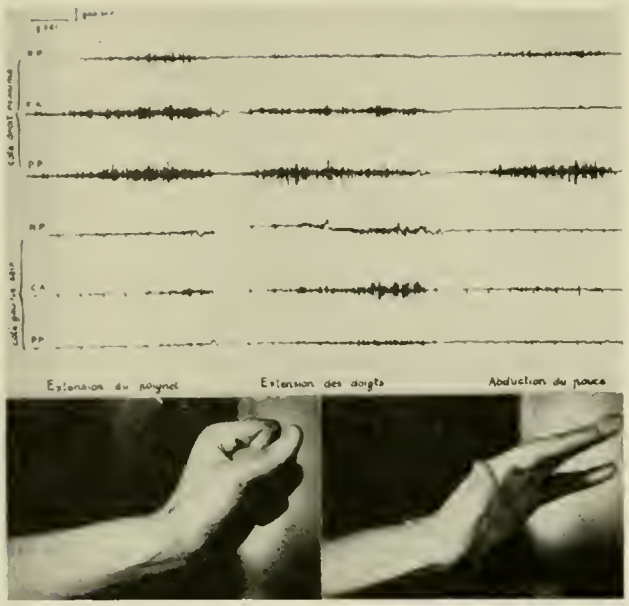



FIG. 11. Electromyographic analysis of the activity of transposed muscles in man after posttraumatic section of the radial nerve. Simultaneous recording on a polygraphic inkwriter of muscular activities recorded by coaxial needle electrodes. The *three upper records* are from the operated right upper limb. *R.P.*, activity of the pronator teres attached to the distal part of the extensor carpi tendon; *C.A.*, activity of the cubitalis anterior transplanted to the tendon of the inactive extensor digitorum; *P.P.*, activity of the palmaris brevis bound to the tendon of the abductor policis. The *three lower records* are from the corresponding muscles in their normal attachment in the left upper limb. The following movements are carried out simultaneously with the two hands. *Left:* Extension of the wrist. Note the cooperation of these three muscles in normal conditions and the parasitic participation of the palmaris brevis in the operated limb. The cubitalis anterior is in this subject the chief executor of this movement. (The *left photograph* shows the fairly good achievement of this movement by the operated hand. The position of the thumb should however be noted.) *Right:* Extension of the digits. Here too a synergistic activity of the palmaris brevis is avoidable only with difficulty by the subject who cannot extend his digits without abducting his thumb. Abduction of the thumb (not illustrated by a photograph) is carried out with quite perfect achievement by the palmaris brevis in the operated side with stabilizing cooperation of the pronator teres. [From Lord (80).]

pointed out by Weiss (130), the lack of secondary adjustment of the hind-limb movements in this species may be correlated with the poverty of pyramidal innervation of the spinal hind-limb centers (110). In the same kind of experiments performed on the forelimb, which is better supplied with pyramidal fibers, an attempt at adjustment by 'trick' performance can be observed; however, a true remodeling of the primitive patterns does not occur at all (110).

Where the rat fails, the monkey partly succeeds; man seems capable of an apparently far better performance. The most carefully analyzed cases, either by clinical (104, 110) or by electrophysiological means (70, 80, 131), are not completely conclusive (see fig. 11). They sometimes have brought to light a real conflict between inborn patterns and newly learned patterns, while at other times these subjects show true voluntary disruption of old existing patterns.

Without doubt man can, by exerting the necessary mental effort and subjecting himself to appropriate training, selectively control certain parts of his musculature, most easily the muscles of the hand. Thanks to his will power he can effectively succeed in correcting certain maladaptations and achieve the proper readjustment of his performance by disrupting primitive patterns. The part played in the success of this process by his corticomotoneural path may obviously be questioned.

Scherb (105), however, noted that a real difference may be observed in the action of transplanted muscles of the lower limb between a single voluntary movement achieved by the patient at rest, on the one hand, and the old patterns of movement which inevitably reappear in an automatic act such as walking. The same type of observations with identical conclusions was made by Weiss & Ruch (132) in a case of functional supernumerary appendages in man. Also, Sperry has rightly pointed out, "To what extent such deliberative corrections could eventually become rapid, automatic and generalized, so as to transfer readily to unpractised activities, can only be guessed at present" (110).

It is therefore obvious that the corticospinal system must be looked upon as the chief mediator of such selective voluntary readjustments. Its anatomical arrangement may account for the accuracy of the cortical control of spinal structures.

With regard to the mechanisms brought into play to achieve the progressive and selective focusing of activity during motor learning, they may be compared with those which are similarly operative in conditioning processes. It would also be interesting to be able to relate the selective localization of voluntary motor activity to that of perceptive attention. These considerations suggest that it might be profitable to search in motor mechanisms for some kind of focalizing mechanisms like those we begin to feel may appear in the organization of sensory systems.

On the other hand, the part played by perceptive or purely sensory regulation should probably be considered as determinant. The accuracy of fine motor adjustments controlled by visual cues, for instance, is much more often limited by perceptual than by motor factors. A possible organization of circuits involved in these sensorimotor relations is diagrammed in figure 10.

AUTOMATIZATION OF THE SKILLED ACT. Thus the first phase of the learning process requires, to a greater or less degree according to the difficulties involved, an important mental effort which mobilizes the higher controlling systems. These, indeed, have at the beginning the heavy task of directing almost every part of the act. From the effort of voluntary control there may result a generalized tension. This tension appears in the musculature in the form of stiffness. It is as though there were a certain diffusion of the motor command, producing parasitic movements which are prejudicial not so much to the precision as to the economy of performance. The mechanism of this diffusion can now be considered (91). On repetition of the act, this initial tension decreases progressively. This decrease in tension seems to be related directly to the degree of participation of the higher control. Voluntary control, as previously stressed, is effected with the help of sensory feedbacks. It is obvious that the first improvements of the performance are attributable to the reorganization of feed-back control. Initially, and as a rule, such feedbacks are chiefly visual in manipulative activities. Then the links between certain sequences in the acts find themselves entrusted to other sensory modalities (chiefly proprioception). Thus, each part of the act becomes the signal which brings the next one into action. The distance receptors are progressively freed from part of their former duties and from voluntary control as well. Then the latter may concentrate on watching over the most delicate parts of the action and thereby improve their performance. Finally, they have to play a part only in bringing the perfectly automatized action into play and turning it off, remaining vigilant, however, to face immediately any emergency beyond the range of flexibility of this automatic act.

The automatic act becomes perfect only when the 'kinetic melody' has, so to speak, its own regulation in hand (45), in other words, when it becomes the output of an organized functional self-regulating unit. This new functional unit owes its structural individuality at least in part to reinforcement and maintenance of new patterns of synaptic linkages. It owes its internal cohesion as well as its own range of flexibility to its 'systemic' organization. Thus, a new skilled act is added to the 'motor repertoire' of the individual.

Where must the stabilization of the learned kinetic system be located in the nervous structures? How can the mechanism of preservation of this pattern be understood? These two questions are still far from being answered satisfactorily. Concerning the location of the learned kinetic patterns in the cortical nervous structures we do not presently possess any decisive experimental evidence (57, 66, 87). That these cortical structures are a part of the kinetic functional unit is, however, not to be doubted. The study of motor apraxias has stressed the pattern-disrupting results of destruction of the anterior cortical motor regions. We have, however, already mentioned the fact that in no place where cerebral tissue may be electrically stimulated can learned purposeful motor acts be obtained. In the same connection, however, it is noteworthy that well-organized memories are activated by stimulation of the temporal region.

Sperry asked "whether the attainment of automaticity by long practice might not result eventually in descent of the central reorganization to lower motor levels" (110). Lashley's earlier data on this point (66), although not conclusive, suggest that the eventual participation of subcortical structures in the learning process could not in any case make an acquired habit independent of its cortical organization. Recently, available data concerning the mechanisms responsible for the 'temporary link' in the Pavlovian conditioning seem to agree in localizing in nonspecific subcortical regions the seat of the so-called 'switching' of such links (42). Nevertheless, such data do not diminish the functional importance of neocortical structures in the process of selective differentiation, concentration and extinction of a conditioned reflex.

The possibility of learning or reorganization within the spinal structures claimed by the organismic school (Anokhin, Goldstein, Bethe) probably remains remote, if ever present, as appears from the pertinent criticisms of Sperry (110, 112). The existence of spinal conditioning is also still definitely controversial (87). The interneural relation patterned by learning would seem to be relegated better to the cerebral circuits and, as proposed by certain authorities, particularly to those circuits connecting the cortical with the subcortical structures.

Concerning the neural mechanisms which must be implicated in the preservation of kinetic patterns, they can only be discussed as yet in a simplified and speculative manner. Hypotheses of two orders seem to have been commonly discussed during recent times. The first emphasize the plastic changes which may occur in neuronal structures either at the molecular level in membranes (60) or at the synaptic surfaces (29). The latter alone is beginning to receive some experimental support (30).

The second stress the cyclic properties of the organization of nervous structures. Closed loops have been seen as the seat of circulating autogenetic activity. Thus, through such circulating impulses, patterns of activity can be prevented from an early disappearance. Such hypotheses have not received conclusive experimental support (94). They still retain, however, sufficient plausibility to be called upon again in connection with the plasticity hypothesis in the most recent nervous theories of learning (29, 47).

We do not have at present any decisive explanation of learning capacity in terms of neurophysiological mechanisms. Owing to the great mass of neurological data which actually falls readily into the traditional scheme of connectionism, acceptable explanations must, at least in part, take this kind of interpretation into account. It seems, however, that the contribution of anatomical factors in determining the patterns of activity should not be overemphasized. Dynamic factors have also an important role to play. As claimed by Sperry, "learning capacity of the nervous system is much more than a mere passive plasticity of a highly impressionable tissue. It is more comparable to the active functional ability of a complex machine" (112). This functional ability inherent in nervous organization as in all living matter remains an important task for future investigations to elucidate.

## REFERENCES


1. Adrian, E. D. *Brain* 66: 89, 1943.
2. Adrian, E. D. and G. Moruzzi. *J. Physiol.* 97: 153, 1939.
3. Akelaitis, A. J. *J. Neurosurg.* 1: 94, 1944.
4. Alajouanine, T. *J. Psychol. norm. path.* 45: 156, 1952.
5. Alix, M. *Ann. sci. nat.* 9: 5, 1868.
6. Altenbürger, H. In: *Handbuch der Neurologie*, edited by O. Bumke and O. Foerster. Berlin: Springer, 1937, vol. III, p. 963.
7. Bartley, S. H. and G. H. Bishop. *Am. J. Physiol.* 103: 159, 1933.
8. Bates, J. A. V. *J. Physiol.* 113: 240, 1951.
9. Beevor, C. E. *Lancet* 1: 1783, 1903.
10. Bell, C. *Phil. Trans.* 2: 163, 1826.
11. Bernard, C. *Introduction à la Médecine Expérimentale.* Paris: Baillière, 1865.
12. Bernhard, C. G. and E. Bohm. *Acta physiol. scandinav.* 31: 104, 1954.
13. Bernhard, C. G. and E. Bohm. *Experientia* 10: 312, 1954.
14. Boreham, J. L., G. O. Kibbler and D. Richter. *J. Physiol.* 109: 17P, 1949.
15. Bosma, J. F. and E. Gellhorn. *J. Neurophysiol.* 9: 263, 1946.
16. Brain, W. R. *Brain* 64: 244, 1941.
17. Broca, P. *Bull. Soc. anat. Paris* (2nd series) 6: 330, 1861.
18. Broca, P. *Bull. Soc. anthrop. Paris* (2nd series) 4: 228, 1869.
19. Brown, G. S. and D. S. Campbell. *Principles of Servomechanisms.* New York: Wiley, 1948.
20. Bucy, P. C. *The Precentral Motor Cortex* (2nd ed.). Urbana: Univ. Illinois Press, 1949.
21. Burns, D. B. *Canad. J. Biochem. & Physiol.* 34: 380, 1956.
22. Chang, H.-T., T. C. Ruch and A. A. Ward. *J. Neurophysiol.* 10: 39, 1947.
23. Craik, K. J. W. *Brit. J. Psychol.* 38: 56, 1947.
24. Craik, K. J. W. *Brit. J. Psychol.* 38: 142, 1948.
25. Dal Bianco, P. In: *Neurologie und Psychiatrie: Festschrift zum 70. Geburstag von Prof. Otto Potzl*, edited by H. J. Urban. Innsbruck: Wagner, 1947, p. 107.
26. Delgado, J. M. R. *Am. J. Physiol.* 171: 436, 1952.
27. Dell, P. *J. physiol., Paris* 44: 471, 1952.
28. Duchenne de Boulogne, G. B. A. *Physiologie des Mouvements.* Paris: Baillière, 1867.
29. Eccles, J. C. *The Neurophysiological Basis of Mind.* Oxford: Clarendon Press, 1953.
30. Eccles, J. C. and A. K. McIntyre. *Nature, London* 167: 466, 1951.
31. Exner, S. *Entwurf zu einer physiologischen Erklärung der psychischen Erscheinungen.* Wien: Deuticke, 1894.
32. Feld, M. In: *Colloque International sur les Malformations congenitales de l'Encéphale.* Paris: Masson, 1958, p. 303.
33. Ferrier, D. *The Functions of the Brain.* London: Smith Elder, 1876.
34. Fessard, A. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer, H. H. Jasper and J. F. Delafresnaye. Oxford: Blackwell, 1954, p. 200.
35. Foerster, O. *Deutsche Ztschr. Nervenh.* 77: 124, 1923.
36. Frank, L. K., G. E. Hutchinson, W. K. Livingston, W. S. McCulloch and N. Wiener. *Ann. New York Acad. Sc.* 50: 187, 1948.
37. Fritsch, G. and E. Hitzig. *Arch. Anat. Physiol.* 37: 300, 1870.
38. Fulton, J. F. *Ohio J. Sci.* 41: 173, 1941.
39. Fulton, J. F. *Frontal Lobotomy and Affective Behavior.* New York: Norton, 1951.
40. Gastaut, H. *Rev. neurol.* 87: 176, 1952.
41. Gastaut, H. *J. physiol., Paris* 44: 431, 1952.
42. Gastaut, H., A. Jus, C. Jus, F. Morrell, W. Storm van Leeuwen, S. Dongier, R. Naquet, H. Regis, A. Roger, D. Bekkering, A. Kamp and J. Werre. *Electroencephalog. & Clin. Neurophysiol.* 9: 1, 1957.
43. Goodby, W. *Brain* 72: 312, 1949.

44. Grunbaum, A. A. *Ztschr. ges. Neurol. Psychiat.* 130: 385, 1933.
45. Guillaume, P. *La Formation des Habitudes.* Paris: Alcan, 1936.
46. Head, H. *Studies in Neurology. 2.* London: Frowde, Hodder & Stoughton, 1920.
47. Hebb, D. O. *The Organization of Behavior.* New York: Wiley, 1949.
48. Hécaen, H. and J. de Ajuriaguerra. *Encéphale* 35: 113, 1942–45.
49. Hécaen, H. and J. de Ajuriaguerra. *Méconnaissances et Hallucinations Corporelles.* Paris: Masson, 1952.
50. Hess, W. R. *Das Zwischenhirn: Syndrome, Lokalizationen, Funktionen.* Basel: Schwabe, 1949.
51. Hines, M. *Biol. Rev.* 18: 1, 1943.
52. Hines, M. In: *The Precentral Motor Cortex* (2nd ed.), edited by P. C. Bucy. Urbana: Univ. Illinois Press, 1949, p. 459.
53. Hines, M. and E. P. Boynton. *Contr. Embryol. Carnegie Inst.* 28: 309, 1940.
54. Hoagland, H. *Science* 109: 157, 1949.
55. Hoff, E. C. and H. E. Hoff. *Brain* 57: 454, 1934.
56. Holmes, G. *Lancet* 203: 59, 1922.
57. Jacobsen, C. F. *A. Res. Nerv. & Ment. Dis., Proc.* 13: 225, 1932.
58. Jasper, H. H. and C. Ajmone-Marsan. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 493, 1952.
59. Jasper, H. H. and W. Penfield. *Arch. Psychiat.* 183: 163, 1949.
60. Katz, J. J. and W. C. Halstead. *Comp. Psychol. Monogr.* 20: 1, 1950.
61. Kohler, W. *Gestalt Psychology.* New York: Liveright, 1940.
62. Laine, E. and C. Gros. *L'Hémispherectomie.* Paris: Masson, 1956.
63. Lairy, G. C. and P. Dell. *Electroencephalog. & Clin. Neurophysiol.* Suppl. 6, 1957.
64. Lansing, R. W. *The Relationship of Brain and Tremor Rhythms to Visual Reaction Time* (Doctoral Thesis). Los Angeles: University of California, 1954.
65. Lapicque, L. *Compt. rend. Soc. de biol.* 109: 1279, 1932.
66. Lashley, K. S. *A.M.A. Arch. Neurol. & Psychiat.* 12: 249, 1924.
67. Lashley, K. S. *Science* 73: 245, 1931.
68. Lashley, K. S. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 529, 1952.
69. Lassek, A. M. *A. Res. Nerv. & Ment. Dis., Proc.* 27: 106, 1948.
70. Lefebvre, J., J. Paillard, G. Lord and J. le Nansek. *Rev. neurol.* 89: 418, 1953.
71. Leroi-Gourhan, A. *Recherches et Débats.* Cahier No. 18: 11, 1957.
72. Leyton, A. S. F. and C. S. Sherrington. *Quart. J. Exper. Physiol.* 11: 135, 1917.
73. Lhermitte, J. In: *Encyclopédie Française* VIII, 28: 6, 1938.
74. Lhermitte, J. *L'Image de Notre Corps.* Paris: Nouvelle Rev. Franç., 1939.
75. Liepmann, H. *Monatsschr. Psychiat. u. Neurol.* 19: 217, 1906.
76. Lindsley, D. B. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 174, 1952.
77. Lindsley, D. B. *Psychol. Rev.* 7: 323, 1956.
78. Livingston, R. B., J. Paillard, A. Tournay and A. Fessard. *J. physiol., Paris* 43: 605, 1951.
79. Lloyd, D. P. C. *J. Neurophysiol.* 4: 525, 1941.
80. Lord, G. *Transplantations tendineuses dans les paralysies radiales traumatiques.* Paris: R. Foulon, 1954.
81. Magoun, H. W. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 480, 1952.
82. Magoun, H. W. *A.M.A. Arch. Neurol. & Psychiat.* 67: 145, 1952.
83. McCulloch, W. S. *Elec. Eng.* 68: 492, 1949.
84. McLean, P. O. *A.M.A. Arch. Neurol. & Psychiat.* 73: 130, 1955.
85. Merton, P. A. In: *The Spinal Cord* (Ciba Foundation Symposium), edited by J. L. Malcolm, J. A. B. Gray, G. E. W. Wolstenholme and J. S. Freeman. London: Churchill, 1953, p. 247.
86. Mettler, R. A. *A. Res. Nerv. & Ment. Dis., Proc.* 27: 162, 1948.
87. Morgan, C. T. In: *Handbook of Experimental Psychology,* edited by S. S. Stevens. New York: Wiley, 1951, p. 758.
88. Morlaas, J. *Semaine hôp. Paris,* 15 février, No. 3, 1929.
89. Mott, F. W. and C. S. Sherrington. *Proc. Roy. Soc., London* 57: 481, 1895.
90. Nielsen, J. M. *Agnosia, Apraxia, Aphasia. Their Value in Cerebral Localization* (2nd ed.). New York: Hoeber, 1946.
91. Paillard, J. *Réflexes et Régulations d'Origine proprioceptive chez l'Homme.* Paris: Arnette, 1955.
92. Pavlov, I. P. *Conditioned Reflexes: An Investigation of Physiological Activity of the Cerebral Cortex.* London: Oxford, 1927.
93. Penfield, W. *Année Psychol.* 39: 1, 1938.
94. Penfield, W. *Brain* 77: 1, 1954.
95. Penfield, W. and H. H. Jasper. *Epilepsy and the Functional Anatomy of the Human Brain.* Boston: Little, 1954.
96. Penfield, W. and T. Rasmussen. *The Cerebral Cortex of Man.* New York: Macmillan, 1950.
97. Phillips, C. G. *Quart. J. Exper. Physiol.* 41: 70, 1956.
98. Pitts, W. and W. S. McCulloch. *Bull. Math. Biophys.* 7: 127, 1947.
99. Poppelreuter, W. In: *Die psychischen Schädigungen durch Kopfschuss.* Leipzig: Voss, 1917, bd. 1, kap. IV.
100. Pribram, K. H. and L. Kruger. *Ann. New York Acad. Sc.* 58: 109, 1954.
101. Pribram, K. H., L. Kruger, F. Robinson and A. J. Berman. *Yale J. Biol. & Med.* 28: 428, 1955.
102. Rapoport, A. *Bull. Math. Biophys.* 10: 145, 1948.
103. Ruch, T. C. In: *Handbook of Experimental Psychology,* edited by S. S. Stevens. New York: Wiley, 1951, p. 154.
104. Scherb, R. *Ztschr. orthop. Chir.* 50: 470, 1928.
105. Scherb, R. *Schweiz. med. Wchnschr.* 19: 354, 1938.
106. Schilder, P. *The Image and Appearance of the Human Body* (Psyche Monogr. No. 4). London: Keegan, Trench, Trubner, 1935.
107. Sherrington, C. S. *The Integrative Action of the Nervous System.* New Haven: Yale Univ. Press, 1906.
108. Sherrington, C. S. *Proc. Roy. Soc., London. ser. B* 97: 519, 1925.
109. Smith, G. E. *The Evolution of Man, Essays.* London: Oxford, 1927.
110. Sperry, R. W. *Quart. Rev. Biol.* 20: 311, 1945.
111. Sperry, R. W. *J. Neurophysiol.* 10: 275, 1947.

112. Sperry, R. W. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951, p. 236.
113. Sperry, R. W. *Am. Scientist* 40: 291, 1952.
114. Stellar, E., C. T. Morganaud and M. Yarosh. *J. Comp. Psychol.* 34: 107, 1942.
115. Szentagothai, J. *J. Neurophysiol.* 2: 445, 1948.
116. Taylor, J. (editor). *Selected Writings of John Hughlings Jackson.* London: Hodder & Stoughton, 1932.
117. Tournay, A. *J. Psychol.* 21: 135, 1924.
118. Tournay, A. *Bull. Psychol. Paris* 8: 597, 1955.
119. Tournay, A. and A. Fessard. *Bull. Ass. fr. avance. sc.* 3: 514, 1945.
120. Tower, S. S. *Brain* 63: 36, 1940.
121. Tower, S. S. In: *The Precentral Motor Cortex* (2nd ed.), edited by P. C. Bucy. Urbana: Univ. Illinois Press, 1949, p. 149.
122. von Bonin, G. In: *The Precentral Motor Cortex* (2nd ed.), edited by P. C. Bucy. Urbana: Univ. Illinois Press, 1949, p. 7.
123. von Kleist, K. *Gehirnpathologie.* Leipzig: Barth, 1934.
124. Wachholder, K. *Willkürliche Haltung und Bewegung insbesondere im Lichte elektrophysiologische Untersuchungen.* München: Bergmann, 1928.
125. Wade, M. *J. Comp. Neurol.* 96: 179, 1952.
126. Wallon, H. *Les Origines du Caractère chez l'Enfant* (2nd ed.). Paris: Presses univ. France, 1949.
127. Walker, A. E. *J. Neurophysiol.* 1: 16, 1938.
128. Walshe, F. M. R. *Brain* 70: 329, 1947.
129. Ward, J. W. *J. Neurophysiol.* 1: 463, 1938.
130. Weiss, P. *Comp. Psychol. Monogr.* 17: Serial No. 88, 1941.
131. Weiss, P. and P. F. Brown. *Proc. Soc. Exper. Biol. & Med.* 48: 1284, 1941.
132. Weiss, P. and T. C. Ruch. *Proc. Soc. Exper. Biol. & Med.* 34: 569, 1936.
133. Wiener, N. *Cybernetics.* New York: Wiley, 1948.
134. Winslow, J. B. *Exposition anatomique de la Structure du Corps humain.* Paris: G. Desprez, 1732.
135. Woolsey, C. N. *Am. J. Physiol.* 123: 221, 1938.
136. Woolsey, C. N. In: *The Biology of Mental Health and Disease* (Milbank Memorial Fund). New York: Hoeber, 1952, p. 193.
137. Yakovlev, P. T. *J. Nerv. & Ment. Dis.* 107: 313, 1948.

CHAPTER LXVIII

# Speech

O. L. ZANGWILL | *The Psychological Laboratory, University of Cambridge, Cambridge, England*

CHAPTER CONTENTS



ALTHOUGH THE ORIGINS of speech remain obscure, its evolution from some primitive form of animal communication is nowadays taken as established. In particular, the discovery by von Fritsch (136) of an elaborate system of gestural communication in the social insects has finally disposed of the view that propositional language is an exclusively human attribute. In the bee at least, communication as concise and explicit as a system of naval signals dominates social organization (102, 127, 136). Recent ethological work further suggests that mechanisms of communication play a far more important role in vertebrate behavior than had previously been supposed (49, 127, 129, 130). Although some authors, such as Revesz (104), deny the relevance of 'animal languages' to the understanding of human speech, communication is nowadays accepted as a biological fact of the first importance.

The mode of evolution of human speech remains wholly conjectural. The limitation of speech in the anthropomorphous apes is usually thought to be due to lack of appropriate specialization within the central nervous system. On the other hand, studies of phonation in the chimpanzee have suggested that absence of speech is more closely dependent on morphological peculiarities of the larynx itself (66). One recent author, however, has argued that transformation of the larynx and the organs of the vocal cavity subserving articulation occurred before the evolution of the hominids (68). This whole matter is deserving of further study.

In the study of human speech, contemporary lines of inquiry are so diverse as to defeat adequate summary. Apart from developments in formal linguistics (cf. 87), psychophysical studies of speech processes have multiplied rapidly in recent years and now dominate an important area of experimental psychology (80, 84–86, 92). The genetic study of language has also shown progress, particularly under the stimulus of Piaget (82, 98). In neurology, aphasia and kindred disorders of speech continue to claim attention and their study has given rise to some fresh concepts of cerebral function (2, 27, 28, 43, 63). On the other hand, neurophysiological studies bearing on speech have been distinctly sparse; there is no general review of the subject in English more recent than that of Kerridge (67) in 1938. This is no doubt due in part to limitations of technique and in part to the prevalent concern of investigators with the wider problems of language and communication, more especially in their technological aspects (37, 86, 117). Although work stimulated by, or related to, com-

munications engineering has produced results of the highest importance, little of it can at present be fitted into the context of traditional physiology. For this reason, information theory will not be considered in the present chapter. Excellent accounts of its contribution to psychophysiology are available elsewhere (86, 87, 117).

## SPEECH PERCEPTION

The understanding of speech is to be regarded properly as a problem in auditory physiology. Unfortunately, our knowledge of the central mechanisms upon which it depends is so fragmentary that no unified account can be given. None the less, a good deal is known as to physical and psychological variables which govern the intelligibility of speech and some, at least, of this information may prove relevant to neurophysiology.

The intelligibility of speech is commonly assessed by the so-called 'articulation testing procedures' (32, 37, 80). A standard series of items (syllables, words or sentences) is presented under controlled conditions and recognition tested by the accuracy of concurrent repetition (articulation score). The material is commonly chosen to reflect the relative frequencies with which the different phonemes occur in everyday speech. It is usual to distinguish the 'threshold of detectability,' i.e. the level of speech at which the listener just hears the speech sounds, from the 'threshold of intelligibility,' i.e. the level at which 50 per cent of the test items are correctly repeated. Standard articulation test scores as a function of the sound pressure level of speech have been established (37).

The detectability thresholds for individual consonant sounds are found to be close to those for pure tones in the middle frequency range but higher than those for single vowels (131). Further, it appears that the 'steady state' portions of phonemic units are not in general sufficient for recognition and certain transition properties must also be utilized (46). In the recognition of vowel sounds, duration, onset characteristics and inflection are relevant characteristics (128). In general, the intelligibility of simple material is mainly a function of the detectability thresholds of the component sounds; but in the case of more complex material grammatical structure, familiarity, context and meaning take on increasing importance. Certain of these variables, in particular context, have been analyzed experimentally with some success in terms of information theory (65, 77, 116).

### *Effects of Stimulus Distortion*

The effects of frequency, amplitude and related types of distortion upon the intelligibility of speech have been widely studied, more especially from the standpoint of communications engineering (37, 80). Some of the findings are of great theoretical importance. Thus it has been established by experiments involving frequency distortion that low frequencies contribute surprisingly little to the intelligibility of speech, despite the fact that they carry most of the speech power. If, for example, all components of speech below 1000 cps are attenuated by a high-pass filter, speech power is reduced by about 80 per cent but articulation score falls by only 10 per cent (39, 80). Equally, experiments involving amplitude distortion have made it clear that the central portion of the speech wave carries essential information for recognition (78, 86). Whereas 'peak-clipping' has surprisingly little effect on recognition, 'center-clipping' virtually destroys the intelligibility of speech. In view of these findings, it has been suggested that intelligibility is best defined as a function of the intensity-frequency-time pattern of the stimulus (80). The significance of this analysis for neurophysiological correlation may well prove considerable.

It has been pointed out by Pumphrey (102) that the transmission of speech through a number of narrow bands, as in the Vocoder system, may effect a virtually complete separation of the emotional and informative aspects of speech. Although intelligibility as such is little, if at all, affected, the quality of speech is greatly altered and little trace of emotional expression may be detected. In general, it would appear that cues relevant to intelligibility are carried within the regions of greatest energy of the spectrum, whereas cues relevant to emotional expression are carried by changes in the fundamental frequency. Pumphrey is therefore led to suggest that a partial dissociation between the emotional and cognitive aspects of speech may have been an important factor in the evolution of human language.

### *Masking of Speech*

The problem of masking, in so far as it has special reference to speech, has been reviewed by a number of authors (55, 72, 84). In the case of masking by tones (pure or complex), the principal finding is that

the intelligibility threshold for speech is markedly raised by low-frequency tones, as might be expected from the phenomena of masking in general. The effect is maximal at and above the frequency of the masking tone. High-frequency tones, on the other hand, have little masking effect. In the case of masking by white noise, the rise in threshold is directly proportional to noise intensity, at least above sound pressure levels of 40 db. The speech-to-noise energy ratio at the masked threshold is broadly constant over a wide range of sound intensities (52).

Masking is generally considered to be a purely peripheral effect. There is however evidence to suggest that it may have a central component (53, 69, 79, 80). Thus Licklider (79) has shown that the phase relations of speech and noise at the two ears affect the intelligibility of speech at any given value of the speech-to-noise energy ratio. More recently, Hirsh (53) has stressed that the binaural masked threshold for speech depends upon the interaural phase relations of the speech and those of the noise; when these are identical, the threshold is high and both speech and noise have the same location. But when the interaural phase relation of the speech is reversed relative to that of the noise, the threshold is low and there is a difference in location. Some relations of masking to recruitment and other factors relevant to clinical audiometry have been examined (17, 54, 55).

*Binaural Speech Perception*

The relations between binaural listening, auditory localization and the perception of speech have been intensively studied. If information is conveyed to the subject simultaneously from two different sources, interpretation of the competing messages is markedly affected by the degree of horizontal separation of the sound sources (15, 16, 101). Further, it has been shown that the effects of feeding two different messages simultaneously, one to each ear, are very different from those that obtain if the same messages are 'mixed' on a tape recording and the two ears stimulated identically (21, 24). In the case of a 'mixed' message, some degree of separation can be effected but interpretation is markedly inadequate. In the case of independent messages, on the other hand, no difficulty is experienced in listening to one or the other message at will or in repeating it concurrently. Under these conditions, however, the subject can report virtually no information conveyed by the 'rejected' message, other than the tongue (English or foreign) and the sex of the speaker ('statistical recognition'). But if both messages are very brief some short-term 'storage' of information may be demonstrated. Thus in an experiment by Broadbent (16) three digits (say 736) were fed to one ear and three different digits (say 245) simultaneously to the other. It was found that the subject could as a rule repeat all six digits correctly, although almost always in the order 736245 or 245736. This phenomenon is interpreted by Broadbent in terms of a short-term storage mechanism adapted to deal with the restrictions imposed upon the organism by limited channel capacity. Some further implications of this view have been discussed (17–19).

The integration of data from the two ears in perception of a unitary 'acoustic field' has been studied by Cherry & Taylor (24). In the first place, they have attempted to measure the time required to 'switch attention' from one ear to the other in listening to simultaneous messages. Their curves relating articulation score to switching frequency are found to show a sharp dip (indicating marked deterioration of recognition) at a switching period of between 0.2 and 0.3 sec. depending on the observer (fig. 1). This dip is held by the authors to mark the transition between switching of attention from ear to ear and binaural listening to what is taken to be unitary speech. At the same time, other explanations of the effect cannot be ruled out. In the second place, they have investigated the range of delay between two identical messages fed independently to the two ears consistent with perception of a single speech source. With delay periods varying between 1 and 50 msec., certain subjective effects of binaural directiveness with apparent shift in location of the sound sources were reported. At an interval of about 15 msec., however, a striking phenomenon is encountered: the hitherto unitary sound source appears suddenly to dissociate into two independent sources of sound (fig. 2). This is of particular interest in so far as the delay period is surprisingly long, far exceeding any period of delay which could occur under natural conditions of audition. Further studies of these and related effects may well throw valuable light on the organization of the 'acoustic field.'

It is most improbable that these various binaural effects in simultaneous speech perception can be explained in terms of masking or related forms of peripheral interference. They would appear to depend on a central selective mechanism closely related to 'attention,' the neurophysiological basis of which is unknown. It is true that some possible

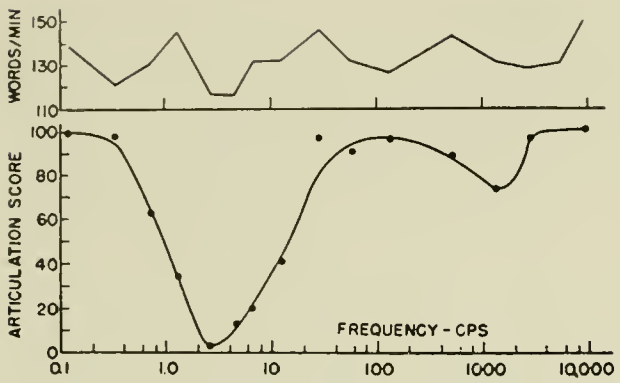



FIG. 1. Articulation score for continuous speech, switched periodically at various frequencies from one ear to the other in one subject. For each ear the proportion of the period occupied by speech is 50 per cent, the remainder being silent. Voltage across telephones, 0.087 volt rms when speech is uninterrupted. [From Cherry & Taylor (24).]

neurological correlates have been adduced, e.g. asymmetry in electrophysiological response in the auditory cortices consequent upon variation in locus of sound-source (109, 133), but their explanatory value is limited. No convincing explanation of binaural speech perception at the neurophysiological level can yet be given.

### *Aural 'Monitoring' of Speech*

The role of aural 'monitoring' in control of speech has been well brought out in a number of recent studies. In 1950, Lee (74) reported that if a subject's own speech is played back to him through closely fitting headphones with a delay of 0.07 to 0.10 sec. ('delayed side-tone'), striking disturbances in speech not uncommonly result. The voice becomes louder; words, syllables and phonemes are repeated; words may be mispronounced; and the overall speech rate is retarded. In some cases, definite signs of anxiety and distress, e.g. palmar sweating, are in evidence. These findings led Lee to conclude that aural feedback normally operates as governor of the overall speech rate. Whereas some subjects appear to slow down automatically under conditions of delayed speech playback, others require practice to achieve the proper cadence. It is in these latter that erratic and stuttering speech may be produced.

Lee's findings have been confirmed and extended by several other investigators (3, 4, 8, 9, 35). Black (8) has reported that both rate and intensity of oral reading are affected by 'delayed side-tone.' In general, he finds, speed of reading is progressively retarded as the increments of delay are increased through the range 0 to 0.18 sec., with a particularly marked effect as delay is increased from 0.03 to 0.06 sec. This might suggest that a delay roughly the same as the duration of a phoneme is of particular significance in retarding the fluency of speech. Further, the fact that the longest reading times are found with delays of 0.18 sec. might be held to indicate a relationship between syllable duration and the effects of 'delayed side-tone.' Black has also adduced evidence that the decreased rate of speaking provoked by

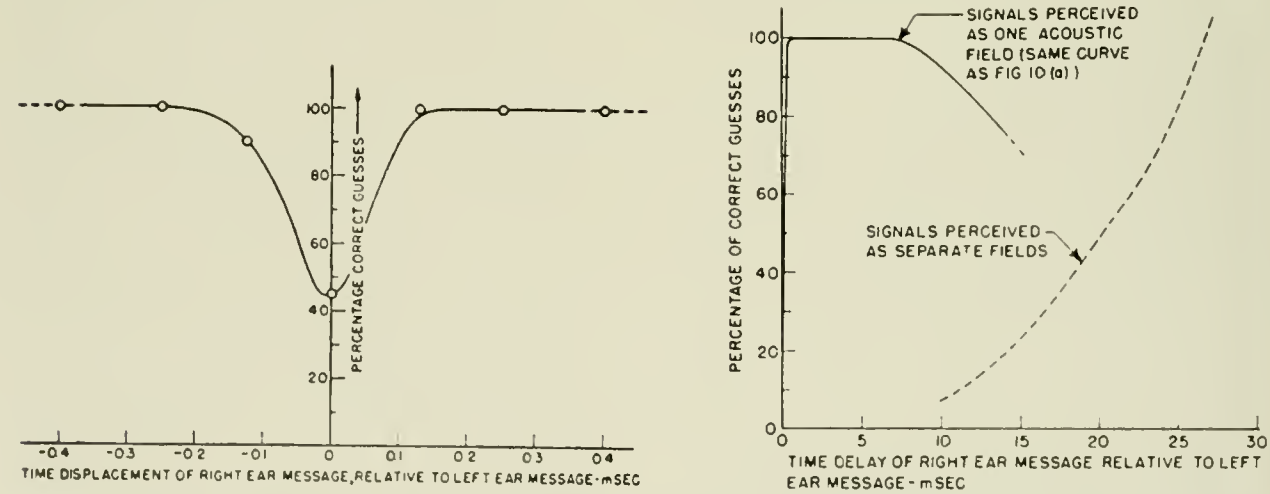



FIG. 2. *Left:* Binaural perception of speech direction (right or left), at various time displacements, of messages to the two ears. *Right:* Binaural perception of one or of two acoustic fields. [From Cherry & Taylor (24).]

'delayed side-tone' may persist for a short period after the latter is removed. This finding is not however confirmed (4). It is also noteworthy that there is typically an increase of vocal intensity with increasing increments of delay, most marked within the range 0 to 0.09 sec. (8). This indicates that delayed speech playback, apart from provoking articulatory disorder, may give rise to significant change in both the speed and intensity of speech.

The results of a more recent study by Fairbanks (35) have confirmed the incidence of changes in both duration and articulation of speech. These changes, unlike the concomitant changes in sound pressure and frequency, are interpreted by this author as primary effects of the time delay. He proposes an index of correct word rate as the most adequate combined measure.

Although the *modus operandi* of aural feedback in the control of speech is obscure, it has been suggested that the mechanism is similar in principle to that of an aurally monitored manual task, such as operating a machine gun (75). If this analogy is sound, one may ascribe the disturbance produced by delayed playback to the fact that the subject is endeavoring to speak at his normal rate but that the delay is sufficient to enable him unintentionally to produce an additional phoneme or syllable. This view gains some support from recent studies of stuttering (22, 23).

## SPEECH PRODUCTION

The production of speech involves highly coordinated movements of the abdominal wall, thorax, larynx, soft palate, tongue and lips. Although under voluntary control, the movements involved in speaking are normally carried out without conscious direction and may be said to constitute highly automatized patterns of reaction. In voiced speech, a regulated expiration forces air past the vocal cords, effectively chopping the air stream into a series of rhythmical puffs (phonation). In the classic view, it is supposed that the vocal cords set up in the adjacent air a complex motion (cord tone), consisting of a fundamental and a large number of overtones (90, 93). This spectrum is then modified in various ways by passage of air through the vocal cavities which are traditionally assumed to operate as simple resonators (vocal resonance theory). In the production of vowel sounds, the tongue is so placed as to approach the roof of the mouth or the back of the throat, thus allowing air to vibrate freely in and out of the resonating cavities. In the production of consonant sounds, on the other hand, the tongue is placed in close apposition to the throat or palate, thus restricting the passage of air. A low turbulence is set up which produces vibrations of considerably higher frequency. In general, the pitch and character of the sounds emitted in phonation may be said to depend upon the varying 'attitudes' of the vocal cords and of the structures involved in articulation.

The vibrating systems produced by the vocal cords and the air columns above them have been subjected to detailed experimental and mathematical analysis (29, 30, 67, 76). Broadly, the results may be said to favor the 'vocal resonance' theory which has also derived support from direct studies of chest resonance in man (67). It has also proved possible to construct synthetic 'speech machines' which effectively duplicate certain aspects of human speech production. The earliest of these were mechanical (93, 105); the more recent, electrical and electronic (30, 31, 47, 124, 126). An adequate short account of 'synthetic speech machines' has been given by Dunn (31).

### *Respiratory Movements in Relation to Speech*

It has been pointed out that the rate of production of the various speech sounds is limited not only by the innervation of the muscle groups concerned but also by the fact that speech is to be regarded as a function 'overlaid' upon respiration (64, 85). Indeed nervous arrangements of some complexity govern the relations of respiration to speech. In normal speakers, there is a fairly close correspondence between abdominal and thoracic movements in breathing, a marked increase in the relative length of expiration during speech, and a certain independence of breathing and vertical movements of the larynx (132). These relations may be markedly altered in cases of speech disorder. In stutterers, for instance, there is not uncommonly opposition between thoracic and abdominal movements in breathing, marked protraction of inspiration, and vertical movement of the larynx synchronous with the movements of respiration (132). It is therefore evident that stuttering, whatever its cause may be, involves widespread incoordination of the entire speech-breathing apparatus.

There is a considerable range of variation between normal speakers in respiratory habit, with some suggestion of a sex difference (67). At the same time, it may be doubted whether peculiarities of voice, such as carrying power, bear any constant relation either to type of respiration or to vital capacity. Type of

respiration also appears to depend in some measure on the rate of speech, with a predominance of abdominal movements at the slower rates (122, 123). Recent studies of breathing activity in conversational speech suggest that both the rate of respiration during speech and the output of speech per expiration are relatively consistent in the same subject. Both indices are however markedly affected by emotion (41, 42).

### *The Vocal Cords*

The appearance of the vocal cords in action has been studied by inspection (direct and stereoscopic), by high-speed motion photography and by the use of various stroboscopic procedures. The earlier results have been reviewed by Kerridge (67); the more recent, by Fletcher (37). Broadly, the results may be said to show that laryngeal movements in speech are decidedly complex and by no means wholly limited to the vocal cords themselves. Thus the false vocal cords are more active than was formerly supposed. The vibration of the cords has both periodic and aperiodic elements, and both cords do not necessarily vibrate at the same rate. Some aspects of vocal cord activity have also been clarified by the use of models (67).

In recent years, the use of high-speed photography has permitted more detailed analysis of vocal cord activity (11, 36, 37). Thus, in a study by Brackett (11), the action of the cords was analyzed by studying the glottal openings during the cycle of vibration, the phase relationship to the cycle, the adjustment of the superior laryngeal structures and the lengths of the glottis on successive frames. With a subject phonating at 256 cps, the cycle of cord vibration showed a phase relationship of one-third closed, one-third opening and one-third closing. There was also evidence that glottal length for a given subject appeared to vary at comparable frequencies and intensities of voice. In general, the results indicate that the movement of the cords is most complex at low frequencies, becoming simpler as the tone is raised until at extremely high frequencies only the edges of the cord adjacent to the glottis are seen to vibrate (37). There is also evidence that the fraction of the cycle time during which the cords remain closed decreases with increasing pitch and that closure of the cords is firmer and more prolonged with increasing intensity of voice. Differences in glottal length, glottal area and in proportion of time allocated to the different phases of the cycle appear to be related to type of voice production and to effects of voice training.

Although the results of these studies have in general supported the traditional theory of vocal cord action, the work of Husson & Dijan (62) might suggest that this theory stands in need of revision. These workers claim that the resonating structures superior to the larynx act essentially by providing an impedance to vocal cord vibration, and they adduce radiological evidence in support of this view. The findings are brought into relation with Husson's theory of direct neurological control of phonation.

### *Neurophysiology of Phonation*

Until recently, it has been generally supposed that the frequency of vocal cord vibration is determined by purely mechanical factors operating at the level of the glottis, e.g. the width of the rima glottidis and the tension and elasticity of the cords. Work by Husson and his associates (40, 58–62, 73, 95, 108, 135) has however suggested that it may prove more correct to regard the larynx as an integrated neuromuscular effector system. The argument is based principally on an experiment by Laget (73) in which vocal cord vibration was successfully induced in the dog by electrical stimulation of the recurrent laryngeal nerve independently of the passage of air through the pharynx, i.e. in the absence of phonation as conventionally defined. It is reported that the stimulated cord approximated suddenly to its fellow, irrespective of its prior position. With stimulus frequencies up to 400 per sec., the rhythm of vocal cord response was found to follow that of the stimulus, although its amplitude varied in a complex fashion with both frequency and intensity. With frequencies above 400 per sec., vocal cord responses were very small and occurred only with high-stimulus intensities. At the same time, Husson and his associates suggest that higher rates of vocal cord vibration may be effected by means of a diphasic (or even triphasic) response mechanism comparable to that postulated by Stevens & Davis in the case of the cochlear nerve (125). Application of these findings to human vocal performance has been attempted (40, 99).

Although the idea of the larynx as a neuroeffector system integrated at bulbar, diencephalic and cortical levels is an interesting one, it cannot be said at present to repose on secure foundations. Repetition of the basic experiments with improved recording technique and more adequate controls is necessary before firm conclusions can be drawn.

*Oral Movements in Speech*

Articulation consists of highly complex movements of the tongue, palate and lips, which constantly vary the size and shape of the nasopharyngeal resonating cavities. Although this has the effect of continually modifying the resulting sounds, it must be borne in mind that it is the movements of articulation alone that give meaning—as opposed to emotional quality—to speech. In suitably trained subjects, this meaning may be appreciated by eye almost as readily as by ear (lip reading). Indeed the actual sounds of speech have been dismissed by Paget (93, 94) as no more than the 'convenient consequences' of articulatory postures which are to be regarded as the primary vehicles of meaning.

The alterations in shape of the air passages above the vocal cords have been studied by a combination of sound films, oscillographic records of the wave forms of speech (sound spectrography), and radiographic examination of the head (62, 67, 100, 110, 111). Thus it has been shown that not all speech sounds entail characteristic lip positions and that there is in general less rigidity in 'vocal posture' than is commonly supposed. For instance, the positions of the tongue formerly deemed essential to the pronounciation of particular speech sounds in fact show considerable variability. Application of these methods to the study of various speech disorders may be expected to produce valuable results.

*Esophageal Speech*

An artificial larynx, of the type devised by the Bell Telephone Laboratories [Fletcher (37)], was at one time widely advocated for use in cases with complete excision of the larynx and the establishment of a permanent tracheotomy. This procedure is open to objection (118, 121), however, and in recent years has been supplanted increasingly by the technique of esophageal speech. In such cases, air expelled from the esophagus may cause the production of sound ('pseudo-voice') through vibration of the contracted edges of the esophagus itself. The mechanism has been carefully studied by Bateman and associates (6, 7) who report measurements of esophageal pressure and chest movements in 3 cases in which the esophageal movements were observed by fluoroscopy. Their observations support the view of Negus (90) that the cricopharyngeal sphincter plays an essential role in the recovery of speech. This sphincter is released when the patient is about to speak, allowing the esophagus to fill. This occurs rapidly in view of the negative intrathoracic pressure to which the esophagus is exposed, reinforced by a firm inspiratory effort. The patient then closes the sphincter and causes the intrathoracic pressure to rise by means of a strong expiratory effort. The resultant rise in esophageal pressure forces some air through the sphincter, producing a sound which is modulated by lip and tongue movements in the usual manner. Bateman *et al.* (7) point out that, although some air is swallowed as a side effect, there is no real evidence that the sound is produced by eructation of air from the stomach, as was maintained by earlier workers (118). The esophagus behaves like a passive tube and it is unnecessary to postulate any activity of its smooth musculature. A modified technique making use of a 'buccal voice' has also been described (134).

NEUROLOGY OF SPEECH

Speech involves a delicate coordination of phonation, respiration, articulation and resonation. Its control may be said to involve all components of the motor system— pyramidal, extrapyramidal and cerebellar—together with those areas of the cerebral cortex presumed to subserve the functions of speech. It is also likely that diencephalic mechanisms are concerned in certain aspects of speech production, more especially in governing speech rate and in control of emotional expression. Possible neurophysiological relationships at the different levels of speech control have been adduced by Husson (61) and Garde (40).

*Bulbar Syndromes*

The laryngeal muscles are supplied by the recurrent branch of the vagus nerve, apart from the cricothyroid which is innervated by the external branch of the superior laryngeal. The corresponding nuclei are in the medulla. Nuclear and infranuclear lesions produce varying degrees of laryngeal paralysis which may or may not affect phonation. Thus a unilateral lesion at any point between the nucleus ambiguus and the recurrent laryngeal nerves causes a unilateral paralysis of the vocal cords, with hoarseness and difficulty in coughing but without loss of phonation. If the lesion is bilateral, on the other hand, both cords are paralyzed and phonation is abolished. In general, lesions at the bulbar level affect phonation rather than articulation, leading to changes in intensity and

quality of voice, shortened duration of phonation, difficulty in enunciating vowels, and rapid vocal fatigue. To this syndrome the name 'neurophonasthenia' has been given by Garde (40).

*Midbrain and Cerebellar Syndromes*

It has long been known that cerebellar lesions, if extensive, are prone to produce defects of speech. This may occur even when the lesion is unilateral, more especially if the vermis is involved (56, 120). The typical disorder consists in staccato or explosive utterance, often with slurring dysarthria or undue separation of syllables (scanning or syllabic speech). It is usually ascribed to an asynergia of the many muscles involved in the act of speaking. This may quite conceivably arise from failure to make proper use of kinesthetic 'feedback' from the speech musculature, as has been argued in the parallel case of cerebellar dysmetria.

A striking disorder of phonation, in some respects unlike cerebellar dysarthria, has been described in certain cases of head injury predominantly involving the midbrain (70). Initially there may be complete mutism, due perhaps to inability to coordinate expiration with closure of the glottis and articulation. With recovery, speech may pass through a stage of forced and ill coordinated whispering before sounds are produced. When voice is regained, it is commonly high-pitched, monotonous and with marked lengthening of vowels quite unlike that ordinarily associated with cerebellar disease. It has been argued by Husson (61) that the rate, expressive intention and emotional quality of speech are normally dependent upon rhythmic discharges at the diencephalic level.

*Apraxic Dysarthria*

As is well known, any lesion within the pyramidal system will, if bilateral, affect speech movements as part of the ensuing paralysis, producing defect or failure of articulation (dysarthria, anarthria). Unilateral lesions, on the other hand, produce no permanent dysarthria and articulation is not affected by hemispherectomy (71). This is taken to imply that the articulatory muscles are innervated from both hemispheres. A lesion within the motor cortex of either hemisphere may, however, affect the movements of speaking as part of a facial dyspraxia (apraxic dysarthria). In this condition, there may initially be complete loss of phonation; with recovery, vowel sounds are as a rule produced before consonants, suggesting that tongue and lip movements are relatively more dyspraxic than those of the larynx. As with apraxia generally, emotional and reactive expression is less affected than volitional speech. The locus of the lesion provoking this syndrome has been stated to be the lower part of the precentral gyrus (89). Although the lenticular zone may be involved to some extent, apraxic dysarthria would appear to be essentially a syndrome of the motor cortex. According to Nathan (89), it is to be envisaged as the highest stage of dissolution of cortical motor function.

*Aphasia*

Whereas speech, physiologically considered, is a pattern of movements, psychologically considered, it is the production of symbols serving in the expression of thought (137). In the light of this distinction, it has been customary to separate defects of articulation from defects of language (aphasia). True, attempts have been made to subsume motor aphasia to apraxia and sensory aphasia to agnosia (81, 139), but these formulations have failed to command general acceptance. For instance, the basic defect in cases of motor aphasia can seldom, if ever, be wholly limited to articulate speech. Thus written expression is commonly as faulty and impoverished as oral speech (138). The disorder would thus appear to transcend mere asynergia or dyspraxia of the articulatory mechanism and to demand reference to the grammatical and syntactical categories of language. Although aphasia may therefore be said to present as a 'psychological' disorder, the modern treatment of linguistic skills as essentially neurological offers hope of escape from the bogy of the mind-body problem and the limitations of traditional dualism (48, 140).

*Phonetic Disintegration in Aphasia*

An attempt has been made in recent years to apply methods of experimental phonetics to the study of aphasia (1, 2, 45). In motor aphasia, emission of phonemes is delayed and often explosive and there may be difficulty in passing from one phoneme to the next, e.g. from consonants to vowels. Tempo, cadence and modulation of speech are uniformly abnormal. It has therefore been inferred that paretic, dystonic and dyspraxic elements constitute the pattern of 'phonetic disintegration.' From the phonetic standpoint, it is interesting to note that no obvious differ-

ence exists between dysarthria and motor aphasia, thus bearing out an old contention of Pierre Marie. It is also noteworthy that disorders in the prosodic quality of speech ('dysprosody') may occur in cases of cerebral lesion without manifest aphasia (88).

*Auditory Defects in Aphasia*

It has long been known that high-frequency deafness in children is apt to produce defects in speech perception hard to differentiate from 'congenital auditory imperception' (34). Recent audiometric studies (1, 115) have established that varying degrees of hearing loss may also occur in acquired aphasias in adults. The loss appears to be more marked in the high-frequency range and may be more severe in the ear contralateral to the side of the lesion (1). It is also more severe in the receptive types of aphasia associated with lesions of the left temporal lobe. These findings have led to the suggestion that lesions involving the transverse temporal gyrus (Heschl's gyrus) may impair auditory perception unilaterally in a manner directly comparable to hemianopia (1). At the same time, a few convincing cases of bilateral 'auditory agnosia' without gross acoustic defect have been reported in the literature (13, 103, 119, 142).

*Aphasia and Cerebral Localization*

Studies of localization in relation to aphasia are limited by a variety of considerations. The clinical manifestations of aphasia are extremely diverse, and no agreed method of classification has as yet been achieved. Further, techniques of anatomical localization are crude and often imperfect. In the case of penetrating wounds, in particular, the full extent of damage can seldom be reliably assessed by the charting techniques in current use (113, 114). None the less, recent work may be said to have thrown fresh light on the hoary problem of the 'speech areas.'

A study by Schiller (114) of 46 cases of penetrating missile wounds of the dominant hemisphere indicates convincingly that disturbances of articulation, inflection and speed of oral speech are most prominent in cases of aphasia in which the stress of the lesion falls upon the foot of the precentral convolution and the posterior extremity of the third frontal convolution (Broca's area). This accords with classic teaching. On the other hand, Conrad (27) presents evidence from 96 cases of penetrating brain injury to suggest that Broca's area is without special significance for articulate speech. Taking the center of the trephine aperture as his criterion of the focus of the lesion, Conrad reports that 'expressive' speech disorders (motor aphasias) are liable to occur with foci anywhere within the boundaries of the excitable motor cortex (areas 4, 6a$\alpha$ and 6a$\beta$ of Brodmann), as shown in figure 3. No significant difference in localization was found as between 'cortical' and 'subcortical' motor aphasia, i.e. motor aphasia and anarthria. Conrad's findings may perhaps be related to reports of limited excision of Broca's area without resultant aphasia (83).

The localization of the 'sensory' forms of aphasia is harder to ascertain in view of the difficulties attending precise definition of these types of speech disorder. There is evidence, however, that the form of aphasia described by Head (48) as syntactical, and marked especially by paraphasic speech, is typically produced by temporal (or temporoparietal) lesions of the dominant hemisphere (27, 48, 114, 138). The foci in cases of 'sensory' and nominal aphasia in Conrad's series are shown in figure 4. As has often been pointed out, the proximity of lesions giving rise to paraphasia to the primary acoustic projection areas may well be a significant factor. Although disturbances of aural comprehension are not invariably present, paraphasia would appear to depend on a defect of high-grade aural control of expressive speech.

The significance of localization for an understanding of the physiology of speech is decidedly

FIG. 3. Localization of lesion in cases of motor aphasia. The *circles* indicate the middle points of the trephine defects: ◖ cortical motor aphasia; ◗ subcortical motor aphasia. [From Conrad (27).]

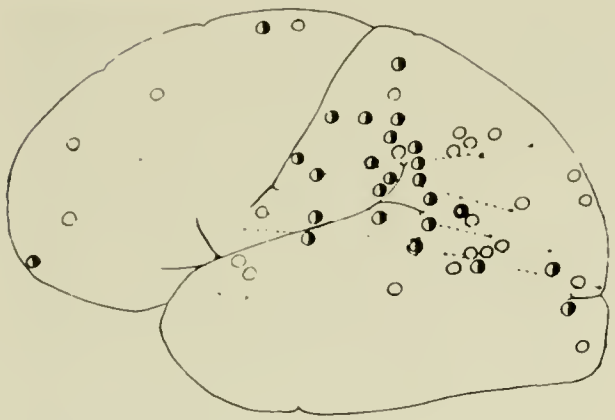


FIG. 4. Localization of lesion in cases of sensory aphasia, together with cases of nominal aphasia: ◑ sensory aphasia; ○ nominal aphasia. [From Conrad (27).]

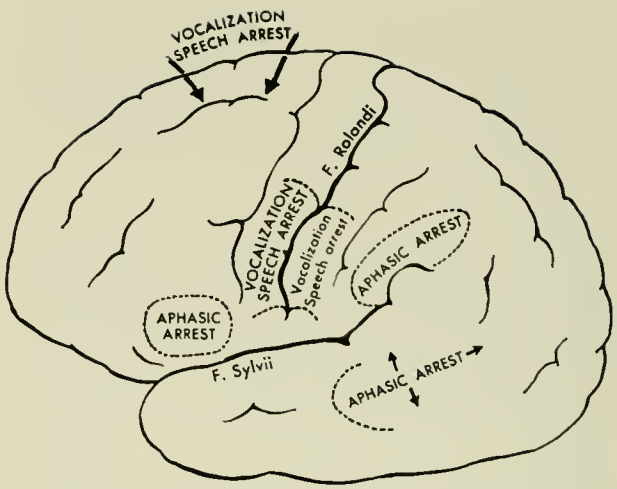



FIG. 5. Summary of areas in which stimulation may interfere with speech or produce vocalization in the dominant hemisphere. [From Penfield & Rasmussen (97).]

controversial (28, 43, 48, 138). As Hughlings Jackson rightly observed, to localize a lesion provoking a disorder of speech does not necessarily imply localization of speech itself. Further, the more recent trend in experimental and clinical neurology is decidedly against any rigid doctrine of cerebral localization of psychological function. None the less, it is scarcely open to doubt that the major central components of linguistic activity involve more or less circumscribed regions of the brain cortex and their subjacent connections. The more strictly executive aspects of language appear closely related to the left inferior frontal cortex, although the critical region may well extend beyond the traditional confines of Broca's area. Word choice and syntax bear a special relation to the temporoparietal cortex and appear closely bound up with the auditory control of speech production. Further, there is evidence that those aspects of language chiefly dependent upon visuospatial orientation, e.g. reading, writing and some aspects of calculation, are largely sustained by the posterior parietal cortex (28, 114). Indeed, it has been argued with some justice that the 'hub' of the essential neural mechanisms subserving thought and speech is to be sought in the temporoparietal region of the dominant cerebral hemisphere (112).

*Induced Vocalization and Speech Arrest*

Following early observations of Foerster (38), Penfield & Rasmussen (96, 97) have established that both vocalization and transitory arrest of speech can be induced in a conscious human subject by appropriate cortical stimulation produced by either a thyrotron or modified Ralun stimulator. As shown in figure 5, vocalization may be elicited by stimuli applied either to the precentral or postcentral gyrus, more particularly the former. It takes the form of a well-sustained vowel sound which cannot be arrested by voluntary effort. Although the cry is evidently primitive, its production involves complex innervation of the abdominal muscles, larynx, pharynx and tongue. But there is no coordinated alteration in tongue and lip position or in expiratory control as would be necessary for articulate speech. Induced vocalization is commonly, though not invariably, associated with some involuntary lip or face movement or, less frequently, with sensory phenomena referred to the mouth or face. The critical region for induced vocalization appears to overlap the sensorimotor representation of the lips, jaws and tongue. It may be induced with equal frequency from either hemisphere.

Repetitive vocalization has been elicited in a small number of cases by stimulation within the longitudinal fissure just anterior to the central fissure (14, 97). This is described by Penfield as superior frontal vocalization.

Arrest of speech has been induced from all areas from which vocalization has been elicited. Speech may be slowed, rendered hesitant or completely

arrested. More interesting, perhaps, is the fact that stimulation of certain additional areas within the dominant hemisphere alone will also provoke speech arrest. This phenomenon is rather more complex, taking the form of transient verbal amnesia or occasionally paraphasic speech ('aphasic arrest'). It may be elicited by stimulation within the inferior frontal, posterior parietal and posterior temporal regions of the cortex (fig. 5). Whereas ordinary speech arrest, as induced by appropriate stimulation of either hemisphere, presents as a transient paresis or dyspraxia of articulation, the inhibition induced by stimulation within the above regions of the dominant hemisphere can be represented as a genuine disturbance of word-finding and speech control. This form of speech arrest is obviously related to true dysphasia, more especially its paroxysmal forms (50).

*Cerebral Dominance*

It has been known since the days of Broca that aphasia and kindred disorders of speech bear a special relation to lesions of the left cerebral hemisphere. This has traditionally been taken to imply a relationship between handedness and control of speech by the hemisphere contralateral to the preferred hand. Although the classical rule relating right-handedness and left cerebral dominance has not been seriously challenged, it cannot now be said that left-handedness necessarily implies comparable dominance of the right hemisphere (27, 33, 44, 57, 106, 107, 141). Whereas it remains true that aphasia from right-sided lesions is much more common in sinistrals than in dextrals, left-sided lesions in sinistrals appear to cause aphasia at least as often as do lesions of the right hemisphere. Indeed the reported cases in which a left-handed patient owes his aphasia to a lesion of the left hemisphere actually outnumber those in which it has been caused by a lesion of the right (44, 141). Left-handedness, therefore, by no means necessarily implies 'right-brainedness.'

These somewhat paradoxical findings have been taken to indicate either that handedness and speech laterality are essentially unrelated (44) or that cerebral dominance is less fully established in sinistrals than in dextrals, aphasia being in consequence liable to follow a lesion of either hemisphere (33, 57). In keeping with the latter interpretation is the fact that severe left-sided brain damage in early childhood seldom significantly retards the development of speech and that later removal of the damaged hemisphere is unlikely to provoke aphasia (5). Further, speech disorders in children are as a rule more transient than in adults and more liable to be provoked by damage to either hemisphere (5). Taken together, the clinical findings suggest some measure of equipotentiality of the two hemispheres in relation to language and the gradual establishment of a gradient of dominance in the early years of life. At the same time, the precise relation of handedness to dominance remains obscure (12).

*Stuttering and Kindred Speech Defects*

It was for many years conventional to ascribe stuttering and related defects to anomalies of cerebral dominance and lack of unified speech control (91, 132). In view of the bilateral central connections of the speech organs, it appeared far from unreasonable to postulate a single, functionally dominant, 'center' in the control of articulate speech. This supraordinate 'center' was identified with Broca's area in the dominant hemisphere. In support of this view might be mentioned the comparative frequency of speech disorders in left-handed individuals, in particular those who have undergone an enforced 'shift' of handedness, and the evidence of widespread and generalized disorganization of motor response in many stammerers (132). At the same time, an explanation along these lines is not without its difficulties and has recently fallen into disfavor. Not all sinistrals — overt or covert — exhibit disorders of speech and stuttering may occur in individuals without any obvious sign of anomalous laterality. Further, emotional difficulties have been implicated in many stammerers, excessive anxiety, in particular, having been repeatedly adduced as a causal factor (10, 20, 25, 51). It would therefore appear that the causation of stuttering and kindred disorders of speech is multiple and unlikely to find explanation in terms of a single mechanism. None the less, there is much to be said for Cobb's view of a 'supracortical' integrative level in speech, disturbance of which may result both from emotional factors and from lack of clear-cut lateral dominance (26).

Impressed by the importance of 'aural monitoring' in speech control, Cherry and co-workers (22, 23) have recently shown that the speech errors of some stutterers can be suppressed by experimental interference with the feedback provided by the speaker's perception of his own voice. Preliminary experiments

indicate that, if a loud tone is applied through headphones to the ears of the subject, thus effectively preventing perception of his own speech sounds, a considerable reduction in stammer is achieved. A similar result is also claimed if the subject is merely required to 'shadow' (i.e. repeat concurrently) a message read by a normal speaker. Although these findings stand in need of confirmation, they at least create the presumption that some forms of stammering arise on a perceptual rather than an executive basis. This might suggest a fresh approach to the elucidation and therapy of the 'functional' speech disorders.

*Development of Speech*

In the acquisition of speech, it would appear that the infant's perception of his own speech sounds plays a most important part in governing motor development. Indeed 'circular reactions' are readily set up in which a speech sound, once spoken, initiates its own repetition. This process no doubt provides the basis for imitation and repetition of the speech of others. The ear-voice 'feed-back loop' would appear of the utmost importance in the monitoring of speech and in providing the basis of orderly speech development. In the adult, it has been suggested that voluntary control of the voice in singing or speaking at a predetermined rate is linked with the activity of the motor area as integrated with a frequency factor of unknown nature provided by the auditory cortex (61). At all events, speech control may readily be envisaged in terms of a whole series of 'feed-back loops,' integrated at various levels and providing the general basis of control of the speed, tempo and rhythm of speech (74). At the highest levels, these reactions are further integrated with processes of symbolic formulation and expression, the nature of which still eludes physiological analysis. But it may be said with complete confidence that the 'language areas' of the dominant cerebral hemisphere comprise the essential machinery of human thought and speech.

REFERENCES


1. Alajouanine, T. *Les Grandes Activités du Lobe Temporal* Paris: Masson, 1955.
2. Alajouanine, T., A. Ombredane and M. Durand. *Le syndrome de desintégration phonétique dans l'aphasie.* Paris: Masson, 1939.
3. Atkinson, C. J. *J. Speech & Hearing Disorders* 17: 419, 1952.
4. Atkinson, C. J. *J. Speech & Hearing Disorders* 18: 386, 1953.
5. Basser, L. S. *Hemiplegia of Early Onset and the Faculty of Speech* (M.D. Thesis). Sydney: Univ. of Sydney, 1956.
6. Bateman, G. H. *Acta oto-laryng.* 43: 133, 1953.
7. Bateman, G. H., A. C. Dornhurst and G. L. Leathart. *Brit. M. J.* 2: 1177, 1952.
8. Black, J. W. *J. Speech & Hearing Disorders* 16: 56, 1951.
9. Black, J. W. *J. Speech & Hearing Disorders* 20: 64, 1955.
10. Bloodstein, O. *J. Speech & Hearing Disorders* 15: 29, 1950.
11. Brackett, I. P. *A.M.A. Arch. Otolaryng.* 47: 838, 1948.
12. Brain, W. R. *Lancet* 2: 837, 1945.
13. Brain, W. R. In: *Neurology* (2nd ed.), by S. A. Kinnier Wilson, edited by A. N. Bruce. Baltimore: Williams & Wilkins, 1955, vol. 3, p. 1413.
14. Brickner, R. M. *J. Neurophysiol.* 3: 128, 1940.
15. Broadbent, D. E. *J. Exper. Psychol.* 43: 267, 1952.
16. Broadbent, D. E. *J. Exper. Psychol.* 47: 191, 1954.
17. Broadbent, D. E. *Proc. Roy. Soc. Med.* 48: 961, 1955.
18. Broadbent, D. E. *Quart. J. Exper. Psychol.* 8: 145, 1956.
19. Broadbent, D. E. *Quart. J. Exper. Psychol.* 9: 1, 1957.
20. Burt, C. *The Backward Child.* London: Univ. London Press, 1937.
21. Cherry, E. C. *J. Acoust. Soc. Am.* 25: 975, 1953.
22. Cherry, E. C., B. McA. Sayers and P. M. Marland. *Nature, London* 176: 874, 1955.
23. Cherry, E. C., B. McA. Sayers and P. M. Marland *J. psychosom. Res.* 1: 233, 1956.
24. Cherry, E. C. and W. K. Taylor. *J. Acoust. Soc. Am.* 26: 554, 1954.
25. Cobb, K. *Ann. Rev. Psychol.* 4: 361, 1953.
26. Cobb, S. and E. M. Cole. *Ann. Rev. Physiol.* 19: 49, 1939.
27. Conrad, K. *Brain* 77: 491, 1954.
28. Critchley, M. *The Parietal Lobes.* London: Arnold, 1953.
29. Curry, R. *J. Physiol.* 91: 254, 1937.
30. Dudley, H. *J. Acoust. Soc. Am.* 11: 169, 1939.
31. Dunn, H. K. *J. Acoust. Soc. Am.* 22: 689, 1950.
32. Egan, J. P. *Laryngoscope* 58: 955, 1948.
33. Ettinger, G., C. V. Jackson and O. L. Zangwill. *Brain* 79: 569, 1956.
34. Ewing, A. W. G. *Aphasia in Children.* London: Oxford, 1930.
35. Fairbanks, G. *J. Speech & Hearing Disorders* 20: 335, 1955.
36. Farnsworth, D. W. *Bell Lab. Record* 18: 203, 1940.
37. Fletcher, H. *Speech and Hearing in Communication.* New York: Van Nostrand, 1953.
38. Foerster, O. In: *Handbuch der Neurologie,* edited by O. Bumke and O. Foerster. Berlin: Springer, 1936, vol. 6, p. 1.
39. French, N. R. and J. C. Steinberg. *J. Acoust. Soc. Am.* 19: 90, 1947.
40. Garde, E. *Rev. laryng.* 74: 255, 1953.
41. Goldman-Eisler, F. *Brit. J. Psychol.* 46: 53, 1955.
42. Goldman-Eisler, F. *Brit. J. med. Psychol.* 29: 35, 1956.
43. Goldstein, K. *Language and Language Disturbances.* New York: Grune, 1948.
44. Goodglass, M. and F. A. Quadfasel. *Brain* 77: 521, 1954.
45. Grewel, F. *Folia phoniat. (Basel)* 3: 100, 1951.

46. Harris, C. M. *J. Acoust. Soc. Am.* 25: 962, 1953.
47. Harris, C. M. *J. Acoust. Soc. Am.* 25: 976, 1953.
48. Head, H. *Aphasia and Kindred Disorders of Speech.* London: Cambridge, 1926.
49. Hebb, D. O. and W. R. Thompson. In: *Handbook of Social Psychology*, edited by G. Lindzey. Cambridge: Addison-Wesley, 1954, vol. 1, p. 532.
50. Hécaen, H. and M. Piercy. *J. Neurol. Neurosurg. & Psychiat.* 19: 194, 1956.
51. Hildreth, G. *J. genet. Psychol.* 76: 39, 1950.
52. Hirsh, I. J. and W. D. Bowman. *J. Acoust. Soc. Am.* 25: 1175, 1953.
53. Hirsh, I. R. *J. Acoust. Soc. Am.* 22: 196, 1950.
54. Hirsh, I. R. *J. Acoust. Soc. Am.* 22: 717, 1950.
55. Hirsh, I. R. *The Measurement of Hearing.* New York: McGraw-Hill, 1952.
56. Holmes, G. *Selected Papers.* London: Macmillan, 1956.
57. Humphrey, M. E. and O. L. Zangwill. *J. Neurol. Neurosurg. & Psychiat.* 15: 184, 1952.
58. Husson, R. *Compt. rend. Acad. sc., Paris* 232: 1589, 1951.
59. Husson, R. *Folia phoniat. (Basel)* 3: 4, 1951.
60. Husson, R. *J. Physiol., Paris* 44: 268, 1952.
61. Husson, R. *Ann. oto-laryng.* 69: 124, 1952.
62. Husson, R. and A. Dijan. *J. radiol. et électrol.* 33: 127, 1952.
63. Kainz, F. *Psychologie der Sprache. 3 Band: Physiologische Psychologie der Sprachvorgänge.* Stuttgart: Enke, 1954.
64. Kaiser, L. *Arch. néerl. phonet.* 10: 121, 1934.
65. Kaplan, A. *An Experimental Study of Ambiguity and Context.* Santa Monica, Calif.: Rand Corp., 1950, p. 187.
66. Keleman, G. *J. Morphol.* 82: 229, 1948.
67. Kerridge, P. M. T. *Physiol. Rev.* 18: 59, 1938.
68. Kipp, F. A. *Experientia* 11: 89, 1955.
69. Kock, W. E. *J. Accoust. Soc. Am.* 22: 801, 1950.
70. Kremer, M., W. R. Russell and G. E. Symth. *J. Neurol. Neurosurg. & Psychiat.* 10: 49, 1947.
71. Krynau, R. W. *J. Neurol. Neurosurg. & Psychiat.* 13. 243, 1950.
72. Kryter, K. D. *J. Speech & Hearing Disorders* Suppl. 1, 1950.
73. Laget, P. *Rev. laryng.* 74: 132, 1953.
74. Lee, B. S. *J. Acoust. Soc. Am.* 22: 824, 1950.
75. Lee, B. S. *J. Speech & Hearing Disorders* 16: 53, 1951.
76. Lewis, D. *J. Acoust. Soc. Am.* 8: 91, 1936.
77. Liberman, A. M., P. Delattre and F. S. Cooper. *Am. J. Psychol.* 65: 497, 1952.
78. Licklider, J. C. R. *J. Acoust. Soc. Am.* 18: 429, 1946.
79. Licklider, J. C. R. *J. Acoust. Soc. Am.* 20: 150, 1948.
80. Licklider, J. C. R. and G. A. Miller. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951.
81. Liepmann, H. *Drei Aufsätze aus der Apraxiegebiet.* Berlin: Karger, 1908.
82. McCarthy, D. In: *Manual of Child Psychology*, edited by L. Carmichael. New York: Wiley, 1946.
83. Mettler, F. A. *Selective Partial Ablation of the Frontal Cortex.* New York: Hoeber, 1949.
84. Miller, G. A. *Psychol. Bull.* 44: 105, 1947.
85. Miller, G. A. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951.
86. Miller, G. A. *Language and Communication.* New York: McGraw-Hill, 1951.
87. Miller, G. A. *Ann. Rev. Psychol.* 5: 401, 1954.
88. Monrad-Krohn, G. H. *Brain* 70: 405, 1947.
89. Nathan, P. W. *Brain* 70: 449, 1947.
90. Negus, V. E. *The Mechanism of the Larynx.* London: Heinemann, 1929.
91. Orton, S. T. *Reading, Writing and Speech Problems in Children.* London: Chapman, 1937.
92. Osgood, C. E. *Method and Theory in Experimental Psychology.* New York: Oxford, 1953.
93. Paget, R. *Human Speech.* London: Paul, 1930.
94. Paget, R. *This English.* London: Paul, 1935.
95. Panconcelli-Calzia, G. *HNO* 3: 129, 1952.
96. Penfield, W. and T. Rasmussen. *A.M.A. Arch. Neurol. & Psychiat.* 61: 21, 1949.
97. Penfield, W. and T. Rasmussen. *The Cerebral Cortex of Man.* New York: Macmillan, 1950.
98. Piaget, J. *The Language and Thought of the Child.* London: Paul, 1926.
99. Portmann, G., R. Humbert, J. L. Robin and P. Laget. *Compt. rend. Soc. de biol.* 149: 296, 1955.
100. Potter, R. K., G. A. Kopp and H. C. Green. *Visible Speech.* New York: Van Nostrand, 1947.
101. Poulton, E. C. *J. Exper. Psychol.* 46: 91, 1953.
102. Pumphrey, R. J. *Acta psychol., Hague* 9: 219, 1953.
103. Reinhold, M. *Brain* 73: 203, 1950.
104. Revesz, G. *The Origins and Prehistory of Language.* London: Longmans, 1956.
105. Riesz, R. R. *J. Acoust. Soc. Am.* 1: 273, 1930.
106. Roberts, L. *Tr. Am. Neurol. A.* 76: 43, 1951.
107. Roberts, L. *Tr. Am. Neurol. A.* 80: 143, 1955.
108. Robin, J. L., P. Laget and J. Vannier. Congrès de l'Association Française pour l'étude de la phonation et du langage, Paris, October 1955.
109. Rosenzweig, M. R. and W. A. Rosenblith. *J. Acoust. Soc. Am.* 22: 878, 1950.
110. Russell, G. O. *J. Acoust. Soc. Am.* 1: 83, 1929.
111. Russell, G. O. *Proceedings of the International Congress of Phonetic Sciences.* London: Cambridge, 1935, p. 198.
112. Russell, W. R. *Lancet* 1: 356, 1948.
113. Russell, W. R. *J. Neurol. Neurosurg. & Psychiat.* 14: 35, 1951.
114. Schiller, F. *J. Neurol. Neurosurg. & Psychiat.* 10: 183, 1947.
115. Schuell, H. *J. Speech & Hearing Disorders* 18: 14, 1953.
116. Shannon, C. E. *Bell System Tech. J.* 30: 50, 1951.
117. Shannon, C. E. and W. Weaver. *The Mathematical Theory of Communication.* Urbana: Univ. Illinois Press, 1949.
118. Stein, L. *Speech and Voice.* London: Methuen, 1942.
119. Stengel, E. and R. E. Hemphill. *J. Neurol. & Psychiat.* 3: 251, 1940.
120. Stenvers, H. W. *Psychiat. neur. bl., Amst.* 25: 237, 1921.
121. Stern, M. In: *Handbuch der Hals-Nasen-Ohrenheilkunde*, edited by A. Denker and O. Kahler. Berlin: Springer, 1929, vol. 5, p. 495.
122. Stetson, R. H. *Arch. néerl. phonet.* 3: 5, 1928.
123. Stetson, R. H. and C. V. Hudgins. *Arch. néerl. phonet.* 5: 1, 1930.
124. Stevens, K. N., S. Kasowski and C. G. M. Fant. *J. Acoust. Soc. Am.* 25: 734, 1953.
125. Stevens, S. S. and H. Davis. *Hearing; its Psychology and Physiology.* New York: Wiley, 1938.

126. Stewart, J. Q. *Nature, London* 110: 311, 1932.
127. Thorpe, W. H. *Learning and Instinct in Animals.* London: Methuen, 1956.
128. Tiffany, W. R. *J. Speech & Hearing Disorders* 18: 289, 1953.
129. Tinbergen, N. *The Study of Instinct.* Oxford: Clarendon Press, 1951.
130. Tinbergen, N. *Social Behaviour in Animals.* London: Methuen, 1953.
131. Tolhurst, G. C. *J. Speech & Hearing Disorders* 19: 28, 1954.
132. Travis, L. E. *Speech Pathology.* New York: Appleton, 1931.
133. Tunturi, A. R. *Am. J. Psychol.* 168: 712, 1952.
134. van Gilse, P. H. G. *Acta oto-laryng.* Suppl. 78: 109, 1949.
135. Vannier, J., R. Saumont, L. Labarrque and R. Husson. *Rev. laryng.* 75, Suppl.: 160, 1954.
136. von Fritsch, K. *The Dancing Bees.* London: Methuen, 1954.
137. Walshe, F. M. R. *Diseases of the Nervous System.* Edinburgh: Livingstone, 1947.
138. Weisenberg, T. H. and K. E. McBride. *Aphasia: A Clinical and Psychological Study.* New York: Commonwealth Fund, 1935.
139. Wilson, S. A. K. *Aphasia.* London: Paul, 1926.
140. Zangwill, O. L. *Psychology as the Study of Behaviour.* London: Cambridge, 1954.
141. Zangwill, O. L. *Advanc. Sci.* 12: 55, 1955.
142. Ziegler, D. K. *A.M.A. Arch. Neurol. & Psychiat.* 67: 323, 1952.

CHAPTER LXIX

# Psychosomatics

PAUL D. MacLEAN | *Laboratory of Neurophysiology, National Institute of Mental Health, Bethesda, Maryland*

CHAPTER CONTENTS



IN ADOPTING the use of the new term 'psychosomatics' the editors of this *Handbook* have taken cognizance of a developing, specialized field of interest in which neurophysiology has joined hands with psychology, psychiatry and internal medicine. The term is here understood to refer to the pursuit of knowledge that is concerned with the explanation of why and how psychological processes find expression through transient or enduring changes within the body. It thus distinguishes a field of study that focuses attention on mechanisms accounting for changes within the body as opposed to those between the organism and its external environment. Stated otherwise, 'psychosomatics' is primarily concerned with the influence of psychological processes on interofective systems.

The recent emphasis on the importance of psychsomatics may be attributed to the growing impression of the medical profession that psychological factors account for a large proportion of illnesses in which the presenting symptoms are physical in nature. It has been inferred that such factors are not only at the basis of a variety of 'functional' disorders, but are also of etiological significance in a number of diseases complicated by single or multiple lesions (68, 70).

## PROBLEM OF TERM 'PSYCHOSOMATIC'

In order to clear the way for meaningful exposition it will be necessary to deal with some semantic prob-

lems pertaining to the word 'psychosomatic,' from which 'psychosomatics' is derived.[1] This will at the same time provide background for considering what constitutes a 'psychological process,' a question that is so fundamental to the 'mind-body' problem and to the methodological approach to psychosomatics.

In an enduring polemic which seems a little dated, one will hear it argued that the term psychosomatic represents a lawless marriage between the words 'psyche' and 'soma.' Now, as in the past, the term continues to be dragged into intellectual court because of breaking the peace of mind of those who contend that it seeds into people's thinking an inadmissible dualism. In spite of this, the marriage has lasted over a 100 years[2] and, because of the popularization it has received by psychiatry and medicine during the past three decades, has gained a wide public acceptance.

Words are tools for thought. The existing definitions of 'psyche' and 'soma' allow sufficient leeway for selection and modification of meanings to permit and justify their continued union for the purpose of conceptualizing the mind-body problem with which we are concerned.

### *Soma*

The word soma itself is easily manageable. If used adjectively in its original meaning, and not in the restricted sense of physiologists, it is entirely suitable for the linguistic purposes of the present discourse. It has become common practice for physiologists to use 'somatic' to distinguish the striated musculature or its controlling systems from the viscera and their regulating agencies. Formerly the word was used to apply only to the body as a whole or, in accordance with Weismann's definition of 1889, to all the tissues of the body exclusive of the germ cells. When so employed, it appropriately embraces the entire 'body viscus' with which psychosomatics is concerned.

### *Psyche*

It is only when proceeding to handle the word psyche and its conjunction with soma that one enters a verbal arena where one must make a real struggle to avoid being impaled on the horns of a dilemma. Psyche stems from the Greek word ψυχή which originally had the same meaning as 'breath' (exhalation, odor). It was a basic concept of both Greek philosophy and physiology that the air (Greek 'pneuma,' Latin 'anima') was a universal, nonmaterial and immortal life principle. Through the process of breathing, organisms drew in this principle, elaborated upon it, and became alive. In other words they became animated matter, as is expressed by the Latin derived word 'animal.' Their sentient part was therefore basically no more than the nonmaterial air that passed back and forth in respiration. Hence psyche (i.e. breath, spirit) became identified with the mental attributes of man and animal. In later times this concept, with certain modifications, found symbolic expression in the Anglo-Saxon word 'soul.'

Except for changed ideas about underlying mechanisms, the present-day concept of the 'psyche' continues to be essentially the same as in Greek times. One thinks of it as referring to the nonmaterial attributes of the mind with all its conscious and unconscious processes. It is this sense of the word that has made the combination of 'psyche' and 'soma' scientifically objectionable. For to say 'psychosomatic' is to imply that the nonmaterial mind can act on the substance of the body.

This objection can be circumvented by taking advantage of the implications in modern definitions of 'psyche.' In the past 100 years the old Greek notion that the 'psyche' is capable of an independent existence has gradually died out, and the mind has come to be looked upon as inseparable from a functioning organic system. Consequently, one can today pick up a standard dictionary and find the psyche defined as "the mind, especially considered as an organic system serving to adjust the total organism to the environment." The definition could have gone a step further and stated that the central nervous system is recognized as being the essential component of the organic system.

### *Psyche as Information*

A further formulation in regard to the psyche will entail the use of the word information. Wiener (69) has suggested that information be considered as orderliness. Stated a little differently, it is the order that emerges from a background of disorder. In an extension of this concept Wiener has pointed out that information is information, not matter or energy. The

[1] In the course of this exposition which represents a new approach to old problems, the reader will recognize that some psychological terms are given connotations quite different from their conventional meanings.

[2] As far as Margetts has been able to discover, the word 'psychosomatic' was first used by Heinroth in 1818 (45). Between then and 1934 he has uncovered 18 authors who subsequently used the term. He notes that "it turns up in a few dictionaries about 1900."

import of this statement can be readily realized by reading aloud any sentence and comparing its meaning with what is obtained when it is read aloud backwards. Although the same amount of energy is expended in each case, the disparity in the amount of information that is obtained is not in itself physically quantifiable. In the light of present knowledge it may be inferred that the central nervous system derives information on the basis of changing patterns of neuronal activity. The patterns are of themselves without substance, but they depend on physicochemical processes within nervous tissue. How the nervous system recognizes these patterns and uses them to make decisions is, of course, a complete mystery.

Before making the next step, it may be well to recall that had it not been for reasoning based on introspection there would be no occasion to be dealing with psychological problems. Through introspection it has been recognized that there are various kinds of information which are subjective in nature and which are variously appreciated in the form of awareness, feelings, perceptions, emotions and thoughts. Figuratively speaking, it was as though the nervous system could hold up the mirror of subjectivity to itself as a means of reflecting information. At the same time it is evident that numerous informational transactions are carried on within the nervous system without a subjective counterpart.

It has been argued that subjectivity is an epiphenomenon which is not essential to what the central nervous system performs. The fact, however, that subjective information represents information over and above what the organism would otherwise have, makes this seem unlikely. In other words the fact that it exists at all means that it is an added source of information which an organism can draw upon in adjusting to its environment. At all events, it must be admitted that it is an important factor in verbal communication between human beings.

### *Definition of Psychological Process and Psyche*

It is the element of subjectivity that most clearly distinguishes psychological from other functions of the nervous system. In the light of this and the foregoing considerations, a psychological process might be inferentially defined as a neuronally determined process which derives information in conjunction with some element of subjectivity and which may or may not use this information to effect a decision. When we come to consider methodological questions, it will be seen that such a definition is compatible with scientific objectivity. For a given organism, the psyche would represent the sum of its transpiring psychological processes in their dynamic relationship with one another. For the sake of emphasis, it will be restated that the informational aspects of the psyche are inseparable from a neuronal substrate. When so understood, the main logical objection to the term psychosomatic is circumvented.

## HISTORICAL NOTE

It is now such accepted practice to consider the role of psychological factors in the diagnosis and treatment of disease that physicians who have trained since the last war find it difficult to realize that psychosomatic medicine is a development only of the past three decades. The lateness in this development can be attributed to the traditional physiological concept that the cerebrospinal and autonomic nervous systems functioned independently of one another. This concept won its way into medical doctrine on the strength of Bichat's *Recherches physiologiques sur la vie et la mort*, published in 1800 (8). Ironically enough, Freud (19), who was to lead a revolution in psychology which has affected practically every facet of modern life, was so indoctrinated with the teaching that the so-called voluntary and involuntary systems functioned independently that he was unable to perceive the application of his theory to one of the most important aspects of human experience and behavior. Consequently, although he could see a ready explanation of how psychological disturbances could lead to hysterical manifestations in parts of the body under the control of the 'voluntary' nervous system, he believed that visceral symptoms could not be psychological in origin.

There were many precedents that were conducive to the ideas expressed in Bichat. First, there were the Greek notions pertaining to the differences between 'animal' and 'vegetative' life; to the role of the four humors in temperament and organ function; and to the magical power of one part of the body to affect another part, including the brain itself, through 'sympathy'. Second, there was Galen's distinction between voluntary and involuntary functions which was later elaborated upon by Fernel, Descartes, Willis, Whytt and others. Third, and most important, was a change in anatomical interpretation that stemmed from Pourfour du Petit's discovery in 1727 that the system of nerves and ganglia related to the viscera was not connected to the brain, as had previously been

supposed, by way of the vagus. This led Winslow, a few years later, to give the new name 'great sympathetics' to the large system of nerves connected with the thoracic and abdominal viscera and to suggest that their ganglia might be looked upon as "so many little brains."[3]

Obviously influenced by Winslow's suggestion, Bichat also referred to the ganglia as little brains. He emphasized that functions relating the organism to the external world (animal life) were dependent on the brain and spinal cord, whereas the organs serving internal functions (organic life) derived nerves from ganglions "and with them the principle of their action." Accordingly, he explained, "I shall henceforward in my descriptions divide the nerves into two great systems, one emanating from the brain, the other from ganglions; the first a single center, the second a very great number." He referred to the latter as the ganglionic nervous system. He developed the argument that everything that pertains to the passions (emotions) pertained to the organic life. He cited how anger affects the heart and circulation, grief the respiration, resentment the stomach and so forth. It therefore followed that the emotions were generated in the internal organs and the 'little brains' controlling them. Consequently, they were beyond the control of the voluntary nervous system.

The first major break with the doctrine of Bichat came near the end of the nineteenth century, with the demonstration by Gaskell in anatomy and Langley in physiology, that the ganglionic nervous system of Bichat (then more generally referred to as the 'vegetative' or 'involuntary' nervous system) was innervated by the cerebrospinal nervous system (61). Their work, however, brought the representation of visceral functions no closer than the midbrain to the supposed level of volition and consciousness in the cerebral cortex. It can be argued that the development of psychosomatic medicine was contingent on the demonstration by subsequent workers that there was a still higher representation of autonomic function in the hypothalamic portion of the diencephalon whose close anatomical relationship with the cortex was well known.

In 1929 in the second edition of his book called *Bodily Changes in Pain, Hunger, Fear and Rage*, Cannon (11) incorporated some of the new findings in regard to the hypothalamus in his well-known emergency theory. Basing his arguments largely on the work of himself, Britton and Bard, he concluded that the hypothalamus, in conjunction with other parts of the diencephalon, served as a center for the elaboration of the experience and expression of emotion. He believed that the cerebral cortex was concerned with emotion only in so far as it could inhibit the aspects of emotion under voluntary control.

Cannon saw in his explanation of central mechanisms of emotion a number of practical suggestions for therapy. As "the cortex has no direct control over the functions of the viscera, it is useless . . . to try to check a racing heart or to lower a high blood pressure, or to renew the activities of an inhibited digestive system by coldly reasoned demand for different behavior." One alternative was to make use of the discretionary powers of the cerebral cortex. Thus an individual could learn to keep away from situations that precipitated his disturbing emotions. Citing Pavlov's work, Cannon also emphasized that the cerebral cortex could inhibit conditioned emotional behavior. Finally, in echoing a conclusion drawn by Breuer & Freud in 1895 (9), he noted, "It is an interesting fact that a full explanation of the way in which a trouble has been caused will not infrequently suffice to remove the trouble, promptly and completely."

In a summing up, Cannon said:

> . . . I have purposely emphasized the physiological mechanisms of emotional disturbances, and for two main reasons. First, I wished to show that these remarkable perturbations could be described in terms of neurone processes. And again, I wished to show that these interesting phenomena need not be set aside as mystical events occurring in the realm of the 'psyche.' It seemed possible that by emphasis on physiological features attention could be drawn to two important reasons for the slighting of emotional troubles, especially by physicians. . . . A too common unwillingness among physicians to regard seriously the emotional elements in disease is due perhaps to the subtle influence of two extreme attitudes and disciplines. On the one hand is the powerful impress of morphological pathology, the study of diseased organs as seen after death. So triumphantly and so generally have the structural alterations which accompany altered functions been demonstrated under the microscope, that any state which has no distinct 'pathology' appears to be unreal or of minor significance. Fears, worries and states of rage and resentment leave no clear traces in the brain. What then, have physicians to do with them? On the other hand, these mysterious and dominant feelings which surge up within us from unknown sources—are they not pure perturbations of the 'psyche'? In that case, what again, have physicians to do with them? . . . An escape from the insistent demands of the pathologist for structural evidence of disease, and also from the vagueness and mysticism of psychological healers, can be found in an understanding of the

[3] See Sheehan's *Discovery of the Autonomic Nervous System* (61).

physiological processes, which accompany deep emotional disturbances. . . . Using the physiological point of view, therefore, I have considered emotions in terms of nerve impulses, much as I might have considered the nerve impulses from the 'motor area' of the cerebral cortex as they govern the movements of skeletal muscles.

As a piece of writing that was both authoritative and popular in its appeal, Cannon's book had a widespread influence. In helping to prepare the way for psychosomatic medicine it made a twofold contribution. First, it increased a receptiveness in the minds of physicians to look upon the importance of psychological factors in bodily disease. Second, it stimulated psychiatrists to see how their theory of the dynamics of the psyche applied not only to mental disorders and hysterical manifestations pertaining to the 'voluntary' nervous system, but also to disorders and disease of structures under the control of the autonomic nervous system (70).

By the middle 1930's the climate of medical opinion was such that the word psychosomatic, given new emphasis by Flanders Dunbar (14), was rapidly seized upon. As early as 1939 there was established a journal called *Psychosomatic Medicine*. In 1942 there was founded the American Psychosomatic Society for research on psychosomatic problems. In the following year there appeared the first textbook on psychosomatic medicine by Weiss & English (68).

### *Psychosomatic Disorders*

To provide background in regard to the role of neurophysiology in psychosomatics, it is necessary to indicate the nature of illnesses that physicians have been predisposed to place in the psychosomatic category. Psychosomatic illnesses may be subdivided into those that are 'functional' and those that are complicated by single or multiple lesions. Each of these groups in turn may be further subdivided according to whether the underlying mechanisms accounting for the changes are considered primarily neural or neurohumoral.

A diagnosis of a psychosomatic functional disorder is usually made after excluding other etiological factors. The patient presents himself with one or more complaints; and if no cause beyond psychological factors can be found to explain the symptomatology, and provided there is no evidence of an underlying psychosis, the condition is labeled as a psychoneurosis. Fatigue, headache, palpitation of the heart, pains around the heart, shortness of breath, nausea, vomiting, indigestion, diarrhea, constipation, backache and joint pains are among the types of complaints that are commonly attributed to functional disorders of psychological origin. Psychological factors are also frequently inferred to be primarily responsible for disturbance of function related to the glands of internal secretion. Disorders of menstruation and lactation may be cited as examples of such. Obesity, which was formerly commonly attributed to glandular dysfunction, is nowadays considered in most cases to result from overeating precipitated by emotional factors.

Finally, there are many illnesses with symptomatologies so well recognized that they can be diagnostically labeled and in which, according to the nature of the disease, there may be tissue changes of a reversible or irreversible nature (70). A partial list of diseases in which psychological factors are considered to be of significant etiological importance includes skin diseases such as urticaria and neurodermatitis, migraine, hay fever, asthma, essential hypertension, peptic ulcer, nonspecific ulcerative colitis, and rheumatoid arthritis. Some physicians have given emphasis to the coincidence of episodes of severe emotional disturbances and the onset of hyperthyroidism and diabetes mellitus.

## ROLE OF NEUROPHYSIOLOGY IN PSYCHOSOMATICS

In considering the role of neurophysiology in psychosomatics, it will be necessary to give further attention to definitions and to point out their significance in regard to some important methodological considerations.

### *Questions of Definition and Methodology*

In the opening section of this chapter, in arriving at a formulation of what is meant by 'psyche' and a 'psychological process,' advantage was taken of Wiener's use of the word 'information.' As information is information, not matter or energy, it is obvious that the informational aspects of the psyche defy physical measurement. It is equally evident that only the individual himself can experience first hand the information he derives from the internal and external environment. The communication of this information to another individual requires that it find expression through some form of behavior. In this respect both man and animal are in the same category, and scientifically, therefore, there is as much justification for submitting the one as the other to psychological

investigation. This should not be taken to mean that both are equally suitable for such study. Man obviously holds an advantage over animals insofar as he is able through verbal behavior to communicate a greater amount of psychological information.

BEHAVIOR AND COMMUNICATION OF INFORMATION. It is implicit in what has just been said that behavior provides a physical correlate of the amount of information in a system. But it remains to be stated what is meant by 'behavior' and 'amount of information.' Behavior may be broadly defined as any change of an entity with respect to its environment. Starting from there, one can proceed, as Rosenblueth *et al.* (57) have done, to subdivide various forms of behavior into a hierarchical system. The more orderly a form of behavior, the greater is its potentiality to convey a greater amount of information, i.e. a greater amount of orderliness.

As McCulloch (47) has pointed out, when information is communicated by some form of behavior there may result a loss of information. He refers to this loss as 'corruption' and defines it as the ratio of information in the input of a system to that in its output. This factor of corruption, or degradation as it might be called, has very important implications in the field of psychosomatic research. The corruption that occurs in the communication of psychological information through the interofective systems is far in excess of that obtaining to the exterofective systems. In other words, the information that one derives from observing and recording the activity of organs, bioelectrical fluctuations of nerve and other tissue, variations in endocrine levels, etc., does not begin to approach what is gained from the external manifestations of an organism's behavior. For this reason, it becomes of the utmost significance in psychosomatic investigation to demonstrate whenever possible a simultaneous correlation between internal and external manifestations of behavior. In dealing with the overt behavioral manifestations of an animal, one is largely confined to observing its vocal, facial and bodily expressions under natural or imposed situations, and to recording its performance of a variety of psychological tests. In the case of man, there is the advantage that, over and above these things, one has recourse to communication through language. Developments in the field of psychiatry have greatly extended the amount of information that may be obtained from man's verbal behavior, as well as his externally manifest nonverbal behavior.

KINDS OF PSYCHOLOGICAL INFORMATION. Finally, these remarks must make an extension of what was said in the introduction about 'kinds' of psychological information. This will require a reliance on what can be reasoned and inferred on the basis of introspective material. Such material may be said to give the greatest amount of information about the psyche. When it is evident from behavioral manifestations that an organism is in a wakeful, responsive condition, it may be inferred that a state of 'awareness' or 'consciousness' exists. Awareness might be said to be the lowest order of subjectively appreciated information. Superimposed on a state of awareness are the various modalities of sensation which become increasingly informative as they are modified by the attributes of quality and intensity and are appreciated in terms of time and space. Dependent on this subjective reservoir are two higher orders of information that are denoted respectively as emotional and ideational in kind.

Information that is ideational in kind may be derived without an intrusive awareness of 'feelings.' It lends itself to communication by symbolic representations that virtually may be linked together in infinite combinations. Information of an emotional kind, on the contrary, manifests itself as distinctive feeling states that give the impression of pervading the body and have the peculiarity of being imbued either with the quality of pleasantness or unpleasantness. Such a verbal description obviously cannot begin to convey what emotional feelings are. Most forms of other sensation can be reproduced for another individual by administering the proper stimulus to his appropriate receptor apparatus, but emotions have no specific gateway to the sensorium. This partially explains the great 'corruption' that occurs when emotion is communicated from one individual to another and the predicament of anyone who tries to define the subjective nature of emotion. As an emotion can be compared only to itself, one can convey its subjective nature to another individual only by denoting the conditions under which it occurs. Fortunately, the behavioral correlates of emotion are sufficiently few and stereotyped as to make this relatively easy to do by word or act.

KINDS OF EMOTIONAL INFORMATION. Unlike ideas, only a limited number of emotions have been identified. All the recognized emotions may be considered from the standpoint of self-preservation and the preservation of the species. Emotions that are informative in

regard to threats to self-preservation or the preservation of the species, and to the eradication of these threats, are characteristically 'unpleasant' in nature. In this category are fear, anger and sorrow. On the other side are pleasurable emotions that are informative of the removal of threats, the active gratification of needs, and the temporary achievement of a state of internal or external homeostasis or both. The emotions of joy and love come conspicuously to mind.

Although, as noted, emotions give the sense of pervading the body, specific emotions are variously felt by different individuals to be more vivid in one or another part of the body. Thus one person may sense the emotion of fear particularly in the region of his stomach; another in his body musculature. Like other forms of sensation, emotional feelings vary in intensity and duration.

A distinction is commonly made between emotions and moods. It can be argued, however, that moods are but various forms of emotion extended in time. A distinction is also frequently made between emotion and anxiety, an unpleasant feeling that accompanies alerting for, and anticipation of, future events. Here again the distinction may be looked upon as being largely arbitrary.

ASSESSING EMOTION IN ANIMALS. Inferences about the emotional states of animals must of course be based purely on nonverbal communication. Through the psychological process of identification man recognizes a number of stereotypes of behavior in animals that he associates with particular emotional states in himself. Lashley (31) points out that fundamental patterns of emotional reaction seem to have undergone little change in mammalian evolution. Fortunately from the standpoint of psychological study this has made it possible to establish certain well-recognized forms of emotional behavior in animals and man, particularly those pertaining to anger and fear and to various forms of gratification.

As will be developed, there are grounds for believing that successively higher orders of information are respectively dependent on neural mechanisms of increasing complexity, all of which, in the intact organism, are mutually related to one another. Hence, it will be indicated that although emotion represents a lower order of information than conceptualized thought, there exists the possibility for reciprocity of action of the underlying mechanisms. Thus emotion may give rise to thought, and thought to emotion. It is also to be pointed out that such a dynamically related hierarchy of systems would allow for upward and downward gradations of awareness that would depend at any one moment on the summed amounts of various forms of information.

### *The Problem for Neurophysiology*

Although it is inherent in what has been said that the clinical specialties are the ones that hold the advantage in getting at the informational aspects of the psyche, there are great limitations clinically in what can be done from the standpoint of investigating the underlying mechanisms. It is in this latter area that neurophysiology, with its access to animal experimentation, is peculiarly suited to making a contribution to psychosomatics.

In order to indicate the nature of the problems in which the aid of neurophysiology is primarily required, it will be necessary again to appeal to introspective material. On the basis of such material it is recognized that emotion is the only form of psychological information which, short of physical exercise, is associated with extensive internal changes of the body. In view of this, it is a matter of first importance to ascertain whether or not one can localize mechanisms in the central nervous system that are particularly concerned with the experience of emotion and its elaboration into behavior. If such mechanisms can be identified and localized, a next step is to inquire how they differ anatomically and functionally from other kinds of neural apparatus. Another major problem in line with this approach is to discover whether or not emotion and its underlying central and peripheral mechanisms can initiate internal changes that are either sufficiently intense or enduring to result in lesions. Here again, in case of a positive outcome, there would follow the need of analyzing the nature of the mechanisms. Questions related to the formation of lesions, their location and chronicity, are among the most challenging ones with which psychosomatic medicine has to deal. The rest of this chapter will take up in order the problems that have been presented and will consider what investigations have thus far contributed or promise to contribute to their solution.

## CENTRAL MECHANISMS OF EMOTION

### *Brain Stem and Spinal Cord*

Comparative neurology indicates that the neural chassis contained within the spinal cord and the brain

stem caudal to the anterior neuropore is essentially similar in all vertebrates. Physiological studies have shown that this neural chassis contains the basic neural apparatus required for posture, locomotion and the integrated performance of mechanisms involved in self-preservation and the preservation of the species. It has long been established that the hypothalamus has neural control over all the interofective systems that account for the visceral and viscerosomatic manifestations which are seen as an accompaniment of emotional behavior. It has been postulated that its neural organization permits the principle of reciprocal innervation to apply to its regulation of sympathetic and parasympathetic activity. In recent years it has been demonstrated that the hypothalamus also exerts a control over the release of pituitary hormones the influence of which on the endocrine systems is so vital to self-preservation and procreation.

It is therefore logical to begin a consideration of central mechanisms of emotion with an evaluation of the emotional capacities of an animal with only its basic neural chassis intact, and an analysis of pertinent material from the standpoint of functional localization.

DECEREBRATE PREPARATIONS. There has been no success in producing chronic preparations of this kind in animals higher than carnivores. Many experiments on carnivores, however, have been complicated by the fact that the preparation had attached remnants of forebrain. Perhaps *cat 228* in Bard & Rioch's study (4) comes as close as any to being suitable for the present analysis. Its behavior was reminiscent of Ferrier's classical descriptions (17) of the decerebrate frog, bird, and rabbit. The observation that stands out in such descriptions pertains to the animal's lack of spontaneity of movement and its failure to investigate its surroundings and to seek nourishment. It resembles nothing so much as an idling mechanism temporarily devoid of its driver. In the case of the cat in question it showed the tendency to remain standing, sitting or crouching for long periods of time, and would fail to eat unless presented with food. There was no grooming nor any signs of fear or pleasure. Undirected angry behavior could be provoked upon noxious stimulation. Characteristically in the decerebrate, the angry behavior is not enduring. Upon cessation of the provoking stimulus the animal will suddenly assume a statuesque posture.

The decerebrate animal shows evidence of sleeping and waking. It will spontaneously assume an appropriate attitude for defecation and urination. Although it will not seek out a partner, it will submit to sexual excitement and perform the copulatory act. If the neuraxis as far forward as the superior colliculus is left intact the female cat is able to manifest estrous behavior, including vocalization and the rest of the 'afterreaction' that occurs following intromission (2).

HYPOTHALAMUS AND MIDBRAIN. Except for the angry and sexual manifestations, it is evident that there is very little in the behavior of a decerebrate animal that can be construed as emotional in character. There is experimental evidence that the structures most crucial to integrating the performance of angry and sexual behavior lie in the hypothalamus and in the central gray and reticulum of the midbrain. More is known in regard to angry behavior. Elements of such behavior have a scattered representation throughout the region in question (28). The classic studies of Bard (1) showed that in decerebrate preparations the posterior hypothalamus must be intact in order to obtain the fully integrated manifestations of rage. As will be indicated, the same requirement does not appear to hold under other experimental conditions. The work of Hess and of Hunsperger has shown that there are principally two regions in the brain stem from which one can elicit full-blown angry behavior in intact preparations. One is in the perifornical region of the hypothalamus (24), the other in the central gray of the midbrain (26). If the latter region is destroyed, the rage response ordinarily elicited by stimulation of the hypothalamus is abolished. On the contrary, destruction of the hypothalamus does not modify the form of the response obtained from the central gray (26). In intact preparations it has been found that chemical stimulation in the region of the central gray will elicit a prolonged state of fury in which the animal will viciously direct his attack (38). From his clinical studies on encephalitis lethargica, von Economo (66) concluded that this region is fundamental to emotional processes.

The decerebrate animal presents a thorny problem in regard to inferences about its subjective state. Can one infer that it is aware and in addition capable of feeling emotion? The angry behavior of such an animal is commonly referred to as 'sham' or 'pseudoaffective' because it is undirected and because it is assumed to be unaccompanied by the 'feeling' of anger. It must be admitted, however, that the behavior of the decerebrate animal in general reveals several characteristics that are recognized as elements of awareness. From the experiments of Magoun and others it can be inferred that the neural apparatus

most crucial to a state of wakefulness, and hence awareness, is contained in the reticulum of the midbrain which is, of course, possessed by the decerebrate animal (43). In regard to the question of emotion only a few observations come to mind, and these pertain to intact preparations. It has been observed that cats which upon chemical or threshold electrical stimulation of the hypothalamus show angry manifestations will nevertheless continue lapping milk (46), or will be submissive to petting and stop to purr and lick the examiner's face between growls (36). As Masserman (46) emphasized, such paradoxical behavior suggests that the animal, although expressing anger, does not 'feel' angry. Using conditioning methods he attempted to obtain information that would allow further inferences about this matter. In brief, he found that cats could not become conditioned to the prospect of receiving electrical stimulation of the hypothalamus with intensities that were just sufficient to elicit signs of angry behavior. He believed these findings supported his original assumption, and he concluded that whereas the hypothalamus serves as an integrator of emotional expression, it is not concerned in the experience of emotion.

With this background in regard to the basic, but limited, contribution of the neural chassis to emotional processes, we turn now to an analysis of the mechanisms of the cerebral 'driver' embodied in the forebrain which evolves forward of the anterior neuropore. This will entail a consideration of the basal ganglia and the cerebral cortex, and their dependent relationship to the diencephalon and other structures of the brain stem.

### *Basal Ganglia*

The basal ganglia of the forebrain are made up of a complex of structures comprising the striatum (putamen and caudate) and the globus pallidus. Johnston (27) gives convincing reasons for not including the amygdala, often considered as 'archistriatum,' as one of the basal ganglia. Edinger (15) referred to the corpus striatum as a "mighty part of the brain which must be of enormous significance; otherwise it would not be present from fishes on upwards. . . ." This portion of the basal ganglia has continued since Edinger's time to be one of the most enigmatic structures of the brain. Considering its size and central location, one wonders if there can be any significant strides in the knowledge of cerebral physiology until more is known about its function. (The present status is presented in Chapter XXXV of this *Handbook*.) Most of the clues about its role in behavior have been given by clinical observations. On the basis of deficits resulting from lesions, it has been inferred that it is essentially a motor apparatus concerned with coordinating postural, locomotor and visceral adjustments involved in all forms of behavior, including, of course, emotional expression. There are intimations from Rogers' ablation studies in pigeons (56) that this purely 'motor' interpretation represents too restricted a view of its activities. He found that pigeons deprived of the corresponding part of the brain could neither retain nor acquire the ability to place in proper sequence their otherwise retained patterns of behavior making up the rituals of mating and nesting behavior. This would indicate that the striatum plays an important role in learning and becomes a reservoir of learned performance. Except for an apparent loss of fear, Rogers could discern no deficits that could be attributed to the deprivation of cortex alone. In contrast to the bird, Bard & Rioch (4) concluded from an analysis of their ablation studies on cats that, in the absence of neocortex and hippocampus, "the striatum plays a very minor role in behavior" and that there is no evidence that in itself it represents a 'center' for the elaboration of emotional activity.

### *Cerebral Cortex*

On the basis of phylogenetic and cytoarchitectural considerations the cerebral cortex can be subdivided into three general types. These may be designated as archicortex, mesocortex and neocortex. The archicortex and the greater part of the mesocortex are contained in the great limbic lobe which lies medially in the cerebrum and surrounds the brain stem. In the evolution of mammals, the neocortex undergoes an exuberant growth with the result that in higher forms it covers over and obscures the 'old' cortex.

NEOCORTEX. The integrity of function of the neocortex depends on its connections with the neothalamus. There is no evidence that the cortex posterior to the central fissure is specifically concerned with emotional behavior. Rather, it appears to elaborate on the sensory data it receives in such a way as to derive information required for behavior that may be succinctly described as intellectual in character. In man, it participates in the elaboration of language.

Forward of the central fissure a wide variety of autonomic effects have been elicited upon stimulation of the so-called 'motor' areas. Observations

made on animals and man in the absence of anesthesia have given no indication that these responses are associated with emotion. It has been suggested that they reflect the cortical integration of supporting autonomic adjustments with existing or anticipated movements of the skeletal musculature. The second possibility has relevance to functions of the neighboring prefrontal cortex and its role in emotion which will now be considered.

In 1936 Fulton and Jacobsen reported on the effects of excising in two chimpanzees the tips of the frontal lobes containing the prefrontal cortex. Their observation that this operation had the effect of alleviating the symptoms of an experimental neurosis in the animal called Becky led Moniz to introduce frontal lobotomy as a treatment for mental illness (20). This once popular procedure has provided a wealth of clinical material pertaining to the functions of the frontal lobes. From an analysis of the data it appears that the prefrontal cortex is a neural elaboration that is primarily concerned with anticipation and planning as it applies to both the self and the species. As far as one is able to judge, the relief of emotional symptoms following lobotomy is primarily attributable to the alleviation of anxiety. As previously noted, anxiety is an emotional state associated with alerting for and anticipation of future events. It might be inferred therefore that emotional guilt feelings are relieved by lobotomy because there is no longer the anxiety that attends anticipation of discovery and punishment for asocial thoughts or acts; that intractable pain, although still experienced, is alleviated because there is no longer the anxiety associated with the anticipation of continued suffering. Similarly, the socially unacceptable behavior which is so frequently seen as one of the undesirable effects of lobotomy might be attributed to an individual's failure to anticipate the consequences of giving expression to his immediate impulses.

In line with the views of Cannon that were referred to in the historical section, it was the consensus prior to 1936 that the diencephalon was the part of the brain that elaborated the experience and expression of emotion. Except for its alleged capacity to arbitrate upon and inhibit the expression of emotion, it was believed that the cerebral cortex did not participate in emotional processes. The new findings in regard to frontal lobotomy led to the assumption that the prefrontal cortex was necessary for the experience of emotion. But a sole emphasis on the prefrontal cortex in this regard was hardly justified in the light of the two following considerations. *a*) Lashley has pointed out that "fundamental patterns of emotional reaction and temperamental types seem to have undergone little change in mammalian evolution. The major changes are rather the result of the development of intelligent foresight and the inhibition of action in anticipation of more remote prospects" (31). *b*) The prefrontal area, in contrast to the phylogenetically old cortex with which we are next to deal, represents one of the cortical formations of the brain that has undergone a very extensive degree of development in the evolution of the mammal.

THE PHYLOGENETICALLY OLD CORTEX. The phylogenetically old cortex comprises the archicortex and the mesocortex. The archicortex and the greater part of the mesocortex are contained in a large cerebral convolution which Broca (10) in 1878 named the great limbic lobe. The term limbic was used to indicate that this lobe surrounds the brain stem. The limbic lobe, as Broca pointed out, is found as a common denominator in the brains of all mammals. As shown schematically in figure 1, the archicortex and mesocortex envelop the ring-like limbic lobe in two concentric bands. The mesocortex, which forms the outer band, makes up most of the superficial cortex of the limbic lobe and extends somewhat beyond its boundaries as perilimbic cortex. In evolution, the inner band of archicortex becomes largely buried through a process of folding; and in higher forms, it undergoes so much displacement by the corpus callosum that the bulk of it comes to lie in the hippocampus in the inferomedial part of the temporal lobe.

Broca emphasized the close evolutionary relationship between the limbic lobe and the olfactory apparatus. This led some authors to refer to this lobe as the rhinencephalon, believing it subserved only olfactory functions. Many physiologists still refer to it as such. The term limbic has the advantage that it is a short and descriptive term and, as Broca pointed out, implies no theory in regard to function.

The nuclear structures associated with the limbic cortex include the hypothalamus, septum, amygdala, anterior and mid-line thalamic nuclei, the habenula, and parts of the basal ganglia. It has become evident that the limbic cortex and its subcortical cell stations comprise a functionally integrated system. In keeping with Broca's terminology, this sytem may be appropriately referred to as the limbic system (34).

In 1937 in a paper called 'A Proposed Mechanism of Emotion,' Papez (51) drew extensively from his own research and the literature to show that a number

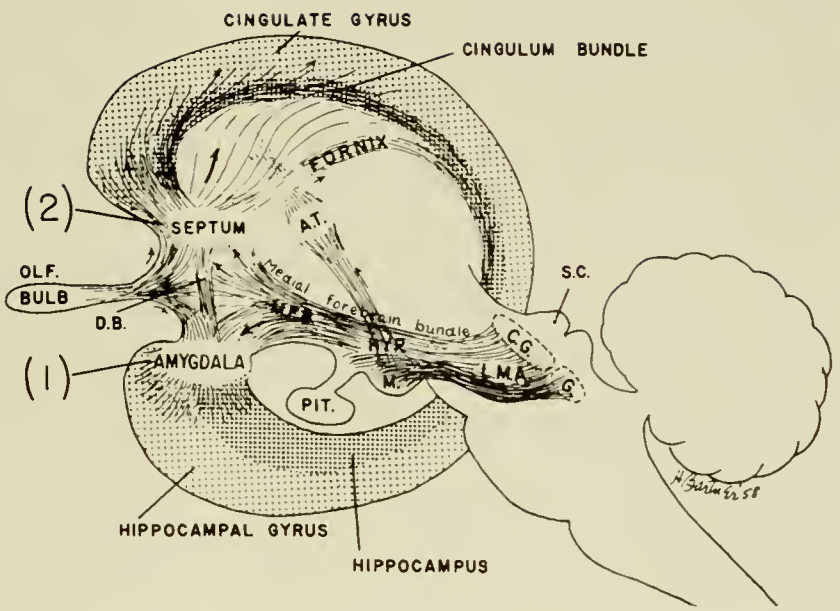



FIG. 1. Schematic drawing, placing emphasis on the medial forebrain bundle (*M.F.B.*) as a major line of communication between the limbic lobe and the hypothalamus and midbrain. The concentric rings of archicortex and mesocortex of the limbic lobe are shown, respectively, in *dark* and *light stipple*. In this diagram only the ascending pathways of the *M.F.B.* are indicated, and attention is focused on the divergence of two streams of fibers to the (*1*) *amygdala* and (*2*) *septum* where there are confluences with fibers from the olfactory apparatus. Limbic structures associated with the amygdala and septum are allegedly concerned, respectively, with self-preservation and preservation of the species. *A.T.*, anterior thalamic nuclei; *C.G.*, central gray of midbrain; *D.B.*, diagonal band of Broca; *G.*, ventral and dorsal tegmental nucleus of Gudden; *HYP.*, hypothalamus; *L.M.A.*, limbic midbrain area of Nauta; *M.*, mammillary body; *PIT.*, pituitary; *S.C.*, superior colliculus. [From MacLean (39).]

of structures making up the limbic system constituted a "harmonious mechanism which may elaborate the functions of central emotion, as well as participate in emotional expression." The kernel of this idea can be found in the writings of Herrick and before him in those of Elliot Smith (35). In 1949 the present author enlarged on the Papez thesis and reviewed the interim developments which tended to support the general validity of his theory (33). Of these the following were particularly notable: *a*) the findings of Klüver & Bucy that in wild monkeys bitemporal lobectomy, provided it included the limbic structures, resulted in apparent tameness, in a compulsive type of oral behavior and in bizarre sexual activity (29); *b*) the work of Spiegel *et al.* (63) and of Bard & Mountcastle (3), concluding that ablations of the amygdala in carnivora led to manifestations of rage; *c*) the reports of Smith (62) and of Ward (67) that bilateral removal of the anterior cingulate portion of the limbic lobe in monkeys was followed by loss of fear and other changes in emotional behavior; *d*) the observations of several workers that autonomic manifestations commonly seen to accompany emotional states could be elicited by electrical stimulation from the entire rostral part of the limbic cortex in both man and animal; and *e*) electroencephalographic findings that in psychomotor epilepsy, in which there is a wide variety of emotional and viscerosomatic manifestations, the epileptogenic focus is frequently found in or near limbic structures at the base of the brain. The majority of these findings have been confirmed, but there is unresolved conflicting evidence in regard to the ablation studies referred to under *b*) and *c*).

Further work has recently begun to suggest that respective portions of the limbic system are predominantly concerned with emotionally determined functions pertaining to the preservation of the self or of the species.

*Self-preservation.* The frontotemporal portion of the limbic system appears to mediate functions that primarily promote the preservation of the self (cf. 34, 35). This region embraces the interrelated mesocortex of the orbital, insular, temporal polar and pyriform areas, all of which have likewise been shown neuronographically to be connected with the amygdala and to the archicortex in the part of the hippocampus lying proximal to the amygdala (54). This group of structures is played upon by a confluence of afferents from the lateral olfactory tract and ascending pathways from the brain stem (cf. fig. 1).

An analysis of stimulation studies in unrestrained and waking animals reveals that the responses obtained from intermixed points in the frontotemporal

region fall principally into two categories. One category includes responses of an alimentary nature such as licking, chewing, retching, etc. In the other category are responses that one associates with the animal's search for food and its struggle for survival. These include sniffing, searching, and angry attack or defense with appropriate vocalization.

Patients who suffer from psychomotor epilepsy as a consequence of epileptogenic foci in this region show parallel manifestations during their seizures. At the same time they have symptoms that lend insight into the subjective functions of this region. In keeping with the automatisms that appear, they commonly experience during the aura alimentary symptoms and vivid emotions. There may be alimentary feelings of thirst, hunger, nausea, etc. The emotional feelings are characteristically self-protective in nature and are therefore unpleasant. Such feelings as fear, terror, dread or anger may be variously associated with a sense of epigastric distress, suffocation, choking or a racing heart. Sometimes there is an alternation of contrasting 'feeling' states, e.g. fear and anger. This suggests there may be a neuroanatomical substratum for the reciprocal innervation of 'feeling' states that compares to the reciprocal innervation of muscles (36).

Bilateral ablations of the frontotemporal region in animals appear to abolish a number of self-preservative functions related to eating and self-protection. As shown by Pribram & Bagshaw (53) in an extension of Klüver & Bucy's classic studies, wild animals appear to become tame and docile after such an operation. They lose their sense of fear and will expose themselves again and again to painful and harmful situations. A monkey which ordinarily eats fruit will eat raw meat or fish. It will put feces, or nuts and bolts in its mouth and sometimes swallow them. In short such an animal loses the ability to look after its self-protection and to eat properly.

From the foregoing findings one is led to infer that the frontotemporal region is largely concerned with survival mechanisms involved in obtaining and assimilating food.

Curiously enough, animals with bilateral ablations of the frontotemporal region, in addition to tameness and docility, reveal exaggerated sexuality that is often bizarre in nature. This was well illustrated by the experiments of Schreiner & Kling (59) in which they removed part of this region in cats. Male cats would indiscriminately mount another male cat, a female dog, a female monkey or even a chicken. These findings suggest that there was a release, in the Jacksonian sense, of other parts of the brain involved in procreative functions.

*Preservation of the species.* This leads to the consideration of another group of related limbic structures that seems to be involved in forms of behavior which, taken together, might be interpreted as being conducive to the preservation of the species rather than the self. As will be indicated, continuing investigation is beginning to suggest that a neural system involving parts of the hippocampus, cingulate gyrus and septum are implicated in pleasure and grooming reactions and in sexual manifestations. Long ago Ramón y Cajal emphasized the close anatomical relationship of these structures (55). As indicated in figure 1, the septal region is a place of confluence for sensory data coming by way of the medial olfactory tract and ascending from the brain stem.

In the course of investigating the structures under consideration the author's laboratory has employed a method (37) that permits simultaneous electrical or chemical stimulation of the brain and recording of the electroencephalographic and behavioral changes in unrestrained and waking animals. Chemical stimulation has usually been carried out by depositing microamounts of cholinergic drugs in crystalline form. Most of the observations have been made on cats. In a study focusing on an intermediate segment of the hippocampus, enhanced pleasure and grooming reactions occurred in association with certain chemically induced and long-enduring electroencephalographic changes. The reader must be referred to the original papers for details (37, 38). Contrary to what is usually the case, male cats would readily submit to genital stimulation, and sustained penile erections could be induced. Occasionally one observed a spontaneous partial erection. Similar sexual manifestations and enhanced pleasure and grooming reactions are also seen following hippocampal after-discharges induced by electrical stimulation. The rat likewise engages in intensive self-grooming for several minutes following electrically induced hippocampal after-discharges, and here too one may note the presence of penile erections.

The investigations on the septum and cingulate gyrus were largely carried out by Trembly, Kim and Lockhart.[4] Enhanced pleasure and grooming reactions were seen in association with chemical stimulation of certain parts of the septum and following after-discharges induced by electrical stimulation. In the

[4] Their as yet unpublished observations are referred to in the literature (36, 38).

latter situation a spontaneous erection was noted on one occasion. The same sexual manifestation has been seen following chemical or electrical stimulation of the anterior supracallossal cingulate and of the cortex just above the posterior cingulate gyrus. The last-mentioned observation calls to mind Erickson's case (16) of hypersexuality in a 55-year-old woman who had a tumor in the paracentral lobule which lies just above the cingulate gyrus.

There are also the following pertinent observations. In 1909, von Bechterew (65) stated that his collaborator Pussep elicited penile erection in the dog upon stimulation in the region of the anterior thalamus. Such stimulation might have involved the anterior thalamic nuclei which are closely related to the cingulate gyrus. In a recent analysis of their extensive material, Hess & Meyer (25) found that the septum was the region where stimulation was most commonly followed by grooming. In 1939 Haterius (23) reported that stimulation in the region of the septum induced ovulation in rabbits.[5]

From the foregoing observations it might be inferred that a portion of the limbic system involving related parts of the septum, hippocampus and cingulate gyrus is concerned with expressive and feeling states that are conducive to sociability and other preliminaries to copulation and reproduction. In other words, this portion of the limbic system, in contrast to the fronto-temporal region, appears to bear on activities that are directed for the purpose of preserving the species rather than the self.

The pleasure, grooming and sexual manifestations that have been described lead one to wonder how they are possibly related to the recent observations of Olds & Milner (50) who found that rats with electrodes implanted in the septum and other limbic structures would repeatedly press a bar to obtain electrical stimulation of the brain. This striking observation has been confirmed by Brady and others. The reader is referred to Chapter LXIII of this *Handbook*, by Brady, for further details.

MASS FUNCTION OF LIMBIC SYSTEM. When a seizure is induced in the hippocampus by local chemical or electrical stimulation, it has the tendency to spread throughout but to be largely confined to limbic and perilimbic structures. As a consequence one has the opportunity in waking and intact preparations to observe the effects of a massive alteration of function in the limbic system. To date such a 'functional ablation' has provided the only means of deriving inferences about the global contribution of limbic function. It is to be emphasized that during hippocampal seizures there may be no appreciable alteration of the bioelectrical activity recorded from the neocortex making up the outer convexity of the brain.

During the stage of culmination of a carbachol-induced seizure in the hippocampus, one has several minutes to observe the effects of such a condition (38). During this stage the behavior of an animal is reminiscent of that seen in the decerebrate preparation. The animal appears semistuporous, shows lack of spontancity of movement, and manifests an incapacity for directed appropriate action in response to various stimuli. Generally there is underreactivity to noxious stimuli of moderate intensity, but intense noxious stimulation elicits a state resembling sham rage that is abruptly followed by the animal's assumption of prolonged statuesque postures when such stimulation is terminated. Basic postural, locomotor and viscerosomatic reflexes are retained.

Conditioning procedures provide a means of obtaining an objective measure of an animal's psychological impairment during propagated hippocampal seizures (41). During brief electrically induced seizures, animals trained in a shuttle box to avoid a shock following the sound of a buzzer fail to respond to the conditioned stimulus, but will frequently direct their escape upon receiving the shock. Relatively simple conditioned reflexes such as a leg withdrawal or changes in cardiorespiratory activity are also abolished by hippocampal seizures. The animal continues, however, to be responsive to the noxious unconditioned stimulus. There is evidence that when there is poor propagation of the discharge to contralateral limbic structures, there may be partial or complete retention of the conditioned response. This suggests that there must be a massive alteration of function in limbic structures of both sides if the animal is to fail altogether in responding to the conditioned stimulus.

## NATURE OF NEURAL APPARATUS INVOLVED IN EMOTION

### *Anatomical Differences*

The question next arises as to how cortical structures that have thus far been experimentally identi-

[5] Since this chapter was written, we have carried out experiments on squirrel monkeys which have been specifically concerned with the localization of genital function in the brain. Points at which electrical stimulation elicits penile erection have been found to follow a course from the septum through the medial preoptic region to the medial forebrain bundle. See MacLean (40).

fied as being important to emotion differ from other parts of the cerebral mantle. First to be considered are some broad distinctions between the limbic cortex and neocortex. The limbic cortex, in contrast to the neocortex, has a wealth of large connecting pathways with the hypothalamus the importance of which in emotional expression hardly needs to be restated. These include the medial forebrain bundle, stria terminalis, fornix and mammillothalamic tract. Recently Nauta (49) has confirmed Ramón y Cajal's findings (55) of a sizeable bundle of fibers in the fornix that project to the tubercle nuclei which sit astride the portal circulation of the pituitary. It has also been learned that the fornix has connections with the central gray of the midbrain (49), the importance of which in emotional behavior is becoming increasingly evident.

Another distinction pertains to cytoarchitecture. The limbic cortex is structurally primitive compared with the neocortex. In broad terms it can be distinguished from the latter by *a*) the absence or poor development of the supragranular layers, *b*) the ending of the afferent plexus in the superficial layers, and *c*) the relative paucity of cells of short axon. Ramón y Cajal looked upon the presence of large numbers of these cells in man's highly evolved cortex as the anatomical expression of the delicacy of function of the human brain.

The neocortex has a topographical representation of the visual, auditory and tactile senses, as well as the proprioceptive sense related to movement. There appears to be but a small representation of viscero-ceptive senses. The preponderant representation of the highly discriminative exteroceptive senses indicates that the functions of the neocortex are principally concerned with refined adaptive adjustments to the external world. On the contrary, comparative neurology indicates that the development of the limbic cortex hinges on the sense of smell which is both an intero- and exteroceptive sense and is presumably chemical in nature. It is a sense that is appreciated largely in terms of quality and intensity and is poorly adapted to giving spatial information. These characteristics would seem to be correlated with the primitive nature of the limbic cortex.

### *Electrophysiological Differences*

Electrophysiologically, as one would expect of highly discriminative senses, rapid on-off responses are recorded in the various sensory areas of the neocortex upon stimulation through the appropriate receptor apparatus. In contrast, olfactory stimulation elicits trains of rhythmically recurring potentials in the pyriform cortex which may persist well beyond the duration of the stimulation. Gustatory and noxious stimulation elicits similar changes in the pyriform area (42). In a somewhat parallel manner stimulation by way of various intero- and exteroceptive systems results in slow rhythmically recurring potentials throughout a large part of the hippocampus (22). These changes may outlast the contrasting low-voltage random fast activity that characteristically appears simultaneously in the neocortex generally. In this connection, and in anticipation of future discussion, it is to be pointed out that stimulation of the reticular formation in the midbrain evokes comparable changes (22).

### *Biochemical Differences*

Recent biochemical and neuropharmacological studies have indicated further distinctions between the limbic and neocortex which have important implications in regard to chemotherapy of mental illness. The 5-hydroxytryptamine content, for example, of the hippocampus and the cortex neighboring the olfactory tracts is far in excess of that found in the neocortex. Radioautographic studies employing $S^{35}$ labeled *l*-methionine have provided indirect evidence that the protein metabolism of the limbic cortex generally, and of the hippocampus in particular, is higher than that of the neocortex (41). In view of these findings it is of interest that the tranquilizing drug reserpine elicits distinctive electroencephalographic changes in the hippocampus, and that these are similar to those seen in ether anesthesia (41).

### *Limbic and Prefrontal Cortex*

From the standpoint of emotional mechanisms it would appear to be significant that the prefrontal cortex evolves in relation to the medial, rather than the lateral, group of thalamic nuclei. Thus its thalamic connections with the dorsomedial nucleus brings it in close association with the anterior and other nuclei of the middle group which are related to the limbic cortex. Neuronographic studies have revealed also that it has corticocortical connections with parts of the limbic cortex falling within the frontal lobe. Its possible reciprocal relationship with the limbic cortex through the reticular system will be discussed subsequently.

*Relevance to Specific Psychosomatic Problems*

PRIMITIVE PSYCHOLOGICAL PROCESSES. The impression is gained clinically that patients with alleged psychosomatic illness show an exaggerated tendency to regard the external world as though it were part of themselves. In other words internal feelings are blended with what is seen, heard or otherwise sensed in such a way that the outside world is experienced as though it were inside. In this respect there is a resemblance to children and primitive peoples. A form of this confusion existing in childhood is morbidly expressed by the following statement of an adolescent girl with epilepsy. Speaking of her first seizure which occurred in childhood upon going into bright sunlight, she said, "I had a funny taste in my mouth of the sun." There are numerous examples in Frazer's *Golden Bough* illustrating how primitive man conceived of various things in the external world as either part of himself or products of himself. In books on psychosomatic medicine one will find an abundance of case material showing comparable tendencies in patients with diseases that are recognized to be greatly influenced by psychological factors (70). The onset of ulcerative colitis has often been noted to bear a relationship to grief. In referring to a recently deceased parent, a patient may point to the belly and say, "He's right here." There may be expressed the feeling of the need to get rid of, to defecate out, what is felt to represent the dead person inside (48).

The alimentary tract appears to be inextricably tied up with these primitive psychological processes, presumably because the mouth provides a natural entrance and the anus a natural exit for what is magically incorporated from the outside world. In this connection food and other edible objects may serve as representations of something in the external world that is desired to be assimilated into the self, or mastered and destroyed like a prey or enemy. The cannabalistic warrior in disposing of his victim takes pains to eat the organs that he associates with strength and other virtues of combat. In psychosomatic medicine, it has been learned through the patient's subjective associations that food may have a multiplicity of meanings in relation to feelings of anger, fear, rejection, grief, etc. A patient with obesity and high arterial pressure said, "I'd eat without realizing it, whenever I would get nervous and upset." Her next associations were to a mean landlady who was making life miserable for her. "It seemed if I could chew up and swallow it, I'd get rid of what was bothering me."

These considerations indicate but superficially the basis for the assumption that primitive psychological processes are at work in psychosomatic illness whereby disturbances in the external world are symbolically internalized and given expression through the mouth, gut and other viscera. As a result environmental disturbances seem to be coped with on a primitive visceral level, instead of being resolved at the higher level of organized thought, speech and action. This is believed by some to be at the core of psychosomatic illness.

PRIMITIVE PSYCHOLOGICAL PROCESSES AND BRAIN MECHANISMS. The psychiatric uncovering of primitive psychological processes in psychosomatic illness requires one to think in terms of cerebral mechanisms that might account for such manifestations. In 1949 in a paper called 'Psychosomatic Disease and the Visceral Brain,' the author (33) considered the anatomy and physiology of the limbic system in the light of this problem. In an elaboration of Papez's proposed mechanism of emotion, emphasis was placed on the cytoarchitectural difference between the relatively primitive limbic cortex and the highly elaborated neocortex. Attention was called particularly to the very primitive character of the hippocampal formation which shows a uniformity of organization from mouse to man (including the overlapping of its afferent fiber systems) and which occupies a strategic position within the limbic system. Reasons were given for the inference that its overlapping afferent systems conveyed sensory data from all the intero- and exteroceptive systems. It was further emphasized that this part of the brain, in contrast to the neocortex, has large connecting tracts with the hypothalamus. These considerations, together with the clinical and behavioral evidence then available, were the basis for the speculation that this limbic cortex interprets experience largely in terms of 'feeling.' It was suggested that the crudity of the analyzing mechanism and the overlapping of incoming impressions from the nose, mouth, viscera, sex organs, eye, ear and body wall might account for the often seemingly paradoxical overlapping of affective reactions, such as those associated with orality and sexuality, as well as the state of confusion between external and visceral awareness that allows outside situations to be experienced as though they were inside.

It was the broad implication of this paper that the limbic lobe, which is found as a common denominator in the brains of all mammals, is also, physiologically speaking, a common denominator of emotional mechanisms, whereas the neocortex might be likened to

an expanding numerator representing in phylogeny the growth of intellectual functions. Such a dichotomy of function it was pointed out, "provides a clue to understanding the difference between what we 'feel' and what we 'know'." To avoid the misleading implications of the popular term rhinencephalon, the limbic lobe and its associated nuclei were referred to as the 'visceral brain.' In its original sixteenth century meaning, 'visceral' pertains to strong inward, and emotional, feelings.

In the light of intervening developments, the ideas set forth in the above paper may still serve as a working hypothesis. Reference is to be made particularly to the electrophysiological studies which have shown that stimulation by way of various intero- and exteroceptive systems elicit rhythmically recurring potentials throughout a large part of the hippocampus. In the forward part of the hippocampal gyrus, gustatory and noxious stimulation evoke rhythmic potentials similar to those brought about by olfactory stimulation. All three of the foregoing senses accent the quality and intensity of a stimulus rather than its spatial relationships. It is also noteworthy that emotion which is frequently experienced in conjunction with discharges in this part of the brain is like the aforementioned forms of sensation insofar as it is registered in terms of quality and intensity. In the light of the affinities of the limbic cortex generally to the type that mediates the sense of smell, might one infer that it interprets experience largely in terms of quality and intensity? The capacity to make purely formal abstractions appears to depend on the evolutionary development of the supragranular layers of the neocortex where one finds a predominant representation of the visual, auditory and tactile senses.

It has been suggested that the organization of the frontotemporal portion of the limbic system may partly account for the psychosomatic condition in which emotional feelings are associated with the alimentary manifestations (34, 35). As already explained, stimulation of intermixed points in this part of the brain elicits alimentary responses and affective reactions that one associates with the animal's search for food and struggle for survival. Patients with epileptogenic foci within or near this region experience during the onset of their seizures emotional feelings in combination with alimentary and other visceral symptoms. A feeling of sadness may be followed by a sense of hunger, a feeling of fear with nausea, etc. It has also been suggested that this primitive part of the brain may account for the primitive psychological process in which food or other edible objects are treated as representatives of what is emotionally disturbing in the environment.

It has been pointed out elsewhere that the emotional feelings of patients with psychomotor epilepsy represent 'raw feeling' insofar as they are not identified with any particular situation or person (34, 35). In other words, they represent 'feeling' out of context. This raises the question as to how specific feelings are related to specific life events. Reasons have been advanced for suggesting that the animalistic brain formed by the limbic system accounts for confusion between the internal world and the external world, and makes possible the brutish stupidity whereby food and other edible objects become mistaken representations for persons or environmental situations. If so, it would seem probable that the connecting up of emotion with reality would depend on the neocortex the functions of which appear to be primarily concerned with precise adaptations to the external world. Most pertinent in this connection is the recognition that conceptualized thought can give rise to emotion and that emotion can give rise to conceptualized thought. As will be pointed out in the final section, this is a fundamental consideration from the standpoint of psychosomatic medicine because the preservation of an environmental event in the form of an idea can perpetuate the emotion associated with that event and thereby lead to a vicious circle.

RECIPROCAL RELATIONSHIP OF LIMBIC LOBE AND NEOCORTEX. Given this hypothetical framework, how might one account physiologically for the reciprocal relationship between the limbic cortex and the neocortex? On the basis of neuronographic studies there appear to be no extensive 'associational' connections between the limbic and the neocortex. This would indicate that the two depend almost entirely on vertical, rather than horizontal, lines of communication. The so-called diffuse projection system of the diencephalon offers one such possible relating system, but the evidence in this regard is still conflicting. There is ample justification, however, for assuming another system of connections through the reticular system of the midbrain. This part of the brain, which has been shown by Magoun and others to be essential to a state of wakefulness, has been found electrophysiologically to bear a reciprocal relationship to both the limbic and the neocortex. In addition there is anatomical and electrophysiological evidence that the central gray, which lies as a core within this reticulum and which plays a dynamogenous role in emotion, is related to

the archicortex. It is therefore conceivable that through the interplay of the neocortex and limbic cortex by way of the central gray and reticulum of the midbrain, thought may generate or inhibit emotion, and emotion may facilitate or paralyze thought. If this were so, it would be expected that this would be one of the neural mechanisms by which the frontal lobes contribute to the anticipatory aspects of emotion. In this connection one might also speculate that a neural circuit is hereby provided whereby an individual can size up his own feelings in such a way as to be able to project himself into the situation of others and to identify his feelings with theirs. Such insight (empathy) is necessary for the foresight that looks to the needs of others, as well as the self.

In the final section there will be an opportunity to consider the indispensable role of memory and learning mechanisms in psychosomatic processes.

In the light of what has been said about the animalistic brain formed by the limbic system, it is probable that even in man it is incapable of dealing with language. In man this would present a problem of communication between limbic and neocortical systems that could be compared to that faced by a rider and his horse:

> Both horse and man are very much alive to one another and to their environment, yet communication between them is limited. Both derive information and act upon it in a different way. At times the horse may shy and bolt for reasons at first inexplicable to his rider. But the patient and sympathetic horseman will try to find out and understand what it is that causes the panic, so he can avoid the disturbing situations in the future or reassure and train the beast to overcome them. One may think of psychotherapy as serving in a similar capacity, helping the intellectual faculties of the patient to ferret out the disturbing factors in his life's situation so they can be dealt with and controlled in an intelligent fashion. In the case of the psychosomatic patient one suspects this helps to prevent excessive 'neighing' on the streets of slow-moving traffic to the viscera (35).

## THE PROBLEM IN REGARD TO FORMATION OF LESIONS

### *Acute Emotional States*

Instances abound in which it has been shown in both animal and man that emotional states precipitated by environmental situations are associated with profound changes of visceral and viscerosomatic activity. For the physiologist, Cannon's book *Bodily Changes in Pain, Hunger, Fear, and Rage* (11) has become a classic reference in this regard. Such observations have led to the little-disputed clinical assumption that chronic emotional disturbances may be concurrently complicated by a variety of functional disorders. Where there is already existing disease, there seems to be no doubt also that in some instances acute emotional states precipitate the formation of a lesion. This appears to be clearly evident, for example, in some cases of coronary thrombosis, and one is reminded of Cannon's demonstration that conditions of emergency are followed by shortening of the clotting time of the blood. But it has yet to be convincingly demonstrated in animal or man that emotional states have an immediate effect of inducing lesions in previously healthy tissue.

### *Chronic Emotional States*

When considering the delayed or chronic effects of emotion, one is faced by a situation complicated by many intervening variables. There is good circumstantial evidence that several alterations of neuroendocrine function which do not manifest themselves immediately are traceable to psychological factors. In discussing 'psychosomatic phenomena' in animals, Beach (5) has offered illustrations of how environmental disturbances appear to have an adverse effect on fertility and lactation. In the field of gynecology and obstetrics, there is abundant evidence that emotional disturbances can be correlated with disorders of the menstrual cycle and of lactation (70). But as in the case of the acute situation, there is no solid evidence that the formation of lesions in healthy tissue can be attributed to the delayed or chronic effects of emotion.

### *'General Adaptation Syndrome'*

In connection with his much publicized 'general adaptation syndrome,' Selye (60) has suggested that psychological 'stress' may precipitate widespread lesions through pituitary adrenocortical mechanisms. The argument is based on the following experimental developments. He found that when rats were exposed to a wide variety of damaging agents, there was a discharge not only of adrenal medullary but also of adrenal cortical hormones, and that concurrently there appeared to be an increase in the animal's resistance to the noxious agents. He saw in this a correlation with the demonstration by Hartmann *et al.* that 'cortin' raised the resistance of tissues to infection. Subsequently it was shown that in the absence of the hypophysis, there failed to be a release of the adrenal

corticoids and that animals showed a poor resistance to all forms of 'stress.' The term stress was used to cover any form of physical insult such as cold, burns, infections, drugs, etc. It was next found that animals maintained on a high sodium and high protein diet and "sensitized by unilateral nephrectomy," developed widespread changes of the connective tissue, arthritis and hypertension following long exposure to such a 'stressful' agent as cold. Similar changes could be produced if the synthetic adrenal hormone desoxycorticosterone was administered instead of the 'stressor' agent. It was argued from this that long continued 'stress' results in a breakdown of the adaptive process whereby a disproportion in the amounts of adrenal glyco- and mineralocorticoids brings about disease. The untoward changes are attributed to a preponderance of hormones having the action of mineralocorticoids. Selye suggests that the "strains and stresses of normal life" can act upon the organism like other "unspecific" stresses, and that when unduly prolonged and severe bring about "diseases of adaptation." From an analogy to the findings in the rat he contends that arthritis, rheumatic fever, periarteritis nodosa and hypertension are among the diseases that may be brought about by psychological or other forms of 'nonspecific stress' in man. This theory has resulted in many heated claims and counterclaims in regard to its validity, and has stimulated investigations which have yielded a wealth of conflicting evidence. The results of investigation in man can be summed up by saying that the findings are contradictory to the particular scheme of hormonal derangement which Selye claims to be at the basis of the above-mentioned diseases (70).

### *Peptic Ulcer*

Of the alleged psychosomatic diseases with lesions perhaps peptic ulcer provides the most convincing clinical and experimental evidence of being etiologically related to emotion. From time immemorial man has been cognizant of a relationship between unpleasant emotional states and disturbances of digestion. Clinically, there has been found such a strong correlation between emotional disturbances and the onset or recurrence of peptic ulcer that great emphasis is given to psychological factors in the therapeutic management of the disease.

Early in the last century William Beaumont (7) made incidental note of the changes of the gastric mucosa and secretions that were seen through the gastric fistula of his patient Alexis St. Martin at times when the latter was fearful or angry. In modern times Wolf and others have taken advantage of cases with fistulas to make a special study of the relation of psychological factors to the condition of the stomach. Such cases admittedly may not be representative of what occurs in unmaimed individuals. In their famous case *Tom*, Wolf & Wolff (71) observed that emotions which were ostensibly related to anxiety, resentment or hostility, were associated with increased gastric vascularity, secretion and motility, whereas there was a reversal of this picture when the patient seemed to be fearful or sad. Other workers have made similar observations in regard to the stomach but have attributed the changes to different emotional factors (70). At this stage of our knowledge, however, it would seem more important to have direct evidence that emotions of various kinds may be accompanied by profound changes in gastric function than to be able to state what kind of change is associated with a particular emotion.

The peripheral mechanism responsible for the formation of ulcers is still not understood. Present opinion is inclined to the view that a combination of factors is involved, including, principally, changes of vascularity and hypersecretion of acid and pepsin. The central nervous system exerts a direct influence on gastric function through vagal and sympathetic pathways. It has recently become evident that it also may have an indirect influence by way of the hypothalamic-pituitary-adrenal axis; cortisone increases gastric secretion, presumably as a result of direct action on the gastric glands (72). Following therapeutic vagotomy in patients with duodenal ulcer, the gastric secretions are reduced to a 'normal' level. This suggests that direct vagal influences are more significant in the disease than indirect humoral factors (72).

In 1932 Cushing (13) published a paper that stimulated much interest in the role of central nervous mechanisms and psychic factors in the pathogenesis of peptic ulcer. Reviewing a large body of literature and drawing upon his neurosurgical experience, he presented arguments for inferring that ulcers are neurogenic in origin and that the morbid processes can be initiated by neural centers in the region of the hypothalamus. He cited experiments showing that gastric erosions could be induced by various manipulations of the vagal and splanchnic nerves, and emphasized Beattie's finding (6) that long-continued stimulation of the tuberal region of the hypothalamus led to small hemorrhagic changes near the lesser curvature of the stomach. His clinical arguments were less con-

vincing insofar as the gastric erosions seen terminally in cases of brain lesions bear no resemblance to those met with in ordinary medical practice. On the basis of the combined evidence Cushing suggested that the hypothalamus provided a mechanism by which psychic factors could precipitate the formation of ulcers.

The role of the hypothalamus in the pathogenesis of ulcers has recently been reinvestigated by French *et al.* (18). They carried out repeated stimulation of the hypothalamus in chronically prepared monkeys and found striking gastric alterations in 6 of 10 animals that were tested. In some instances there were focal ulcerations characterized as "large, raised edematous lesions with deep purple coloration and gray necrotic center." In an earlier series of investigations, it had been demonstrated that hypothalamic stimulation brought about a quick increase in gastric secretion by way of the vagus and a delayed increase through the activation of pituitary-adrenocortical mechanisms. Mahl (44) has reported that chronic fear, as opposed to acute fear, is associated with an increase in gastric acidity in dogs and monkeys. No gastrointestinal lesions were found in his animals.

### *Experimental Failure to Induce Lesions*

POSSIBLE EXPLANATION. It has been shaking to concepts of psychosomatic medicine that thus far animal experimentation has failed to show a causal relationship between emotional states and the formation of lesions in the gut or elsewhere in the body. But there is the possibility that in such investigation the emotion-inducing conditions have not been sufficiently drastic and continuous. That this is indeed the case is suggested by recent studies (58). Some observations made in the author's laboratory bear on this problem. It was found in the process of establishing conditioned cardiac and respiratory responses in cats that if the tests (in which a shock was used as the unconditioned stimulus) were administered more than every 5 min., the cardiac and respiratory rates failed to return to the base-line level. On the contrary, the heart and respiratory rates became and continued so fast throughout a training session that one could distinguish no differential changes at the time of a test. The same situation appeared in the macaque with the exception that after the first few tests, no amount of elapsed time between tests conducted in the course of a morning was sufficient to allow the signs of sympathetic overactivity to abate. This indicates that there was a factor of anticipation that kept alive the animals' response to the test situation. Phylogenetic considerations, together with what is known about the functions of the prefrontal cortex, are suggestive that differences in the development of this part of the brain in the cat and monkey may partially account for the temporal discrepancies in their behavior in the above situation. In other words, it might be supposed that phylogenetically with the progressive development of the prefrontal cortex the animal acquires an increased capacity to anticipate the recurrence of an event and, through the neurological substitution of the idea of the event for the event itself, to keep alive the physiological changes that were precipitated by it. From the standpoint of psychosomatic illness and the potentiality of lesion formation, this would perhaps account for a fundamental difference between man and animals. At all events, in the design of animal experiments it would seem of great significance to keep these factors in mind.

SUGGESTIONS IN REGARD TO FURTHER RESEARCH. In further research along these lines conditioning techniques would appear to offer particular promise as a means of inducing enduring visceral and viscerosomatic changes. It was first observed by Pavlov (52) that in the course of conditioning procedures, some dogs developed signs of what has since been classically referred to as an experimental neurosis. In the United States, Gantt and Liddell have for several years devoted study to experimental neurosis and have identified a number of conditioning procedures that are conducive to its development.

*Problem of specificity.* Liddell and co-workers have made some notable observations on sheep and goats that may furnish a lead for investigations on the problem of lesion formation, as well as the problem of specificity. The latter problem pertains to the question of why in a given case the symptoms and signs of an allegedly psychosomatic illness are localized to a particular organ or system of the body. For example, why is it that one patient acquires a peptic ulcer whereas another develops high arterial pressure? Or again, why is it that in the same individual symptoms of peptic ulcer may predominate at one time and those of hypertension at another? Thus far there has been a failure to relate the manifestations of a particular disease to a particular personality structure or to a particular psychological condition or to other factors (12). Liddell and his group found that in some animals the administration of conditioning tests at monotonously regular intervals led to unmistakable signs of an experimental neurosis (32). Curiously enough, the animals that were tested at 2-min. intervals seemed

to develop predominantly parasympathetic manifestations, whereas those tested at 5-min. intervals showed signs of sympathetic overactivity. In investigations following up this interesting lead it will be of particular interest to discover whether or not, with more prolonged testing, lesions might eventually appear in the variously affected systems.

*Learning and memory.* Conditioning methods also have the potentiality of helping to identify neural mechanisms of learning and memory that are conducive to psychosomatic dysfunction. It has been suggested that learning and memory depend on the integration of internally and externally derived experience (30). If so, there are indications that this would require the integration of the performance of dissimilar mechanisms because conditioning procedures reveal that visceral and locomotor systems are differentially affected in the learning process. Indiscriminate visceral responses regularly appear before an animal learns a discriminative act. Furthermore, in classical trace conditioning in which there is an interval of several seconds between the cessation of the conditioned stimulus and the onset of the emotion-inducing unconditioned stimulus, one can readily establish conditioned cardiac and respiratory responses, but not a specific leg response. On the contrary, in conditioning where there is a temporal overlap of the conditioned and unconditioned stimuli, a leg response is rapidly acquired.

Such discrepancies have important implications in regard to learning and the incipience of psychosomatic disorders. It is recognized, for example, that in the house training of a dog, one must punish the animal immediately after it soils or it will fail to learn the significance of the punishment, and may subsequently cower and cringe every time it sees its master. In other words, it fails to discriminate that the only time it needs to fear the hand of authority is when there has been a specific misdeed. In human affairs, a parallel situation is suggested by the mother who habitually postpones punishment of a child until the father can return home to administer the whipping. Conceivably, such circumstances would be conducive to the formation of indiscriminate visceral reactions in childhood. Furthermore, through the symbolic process, the father would stand in the position to become interchangeable with all authoritative figures who in turn would be feared regardless of the circumstances in which they appeared (41).

How is it to be explained that in trace conditioning which calls for the association of two temporally separated events, cardiac and respiratory responses are readily conditioned whereas a specific leg withdrawal is not? It is possible that the dichotomy in function of limbic and neocortical systems bears on this question. As already emphasized, the limbic cortex is strongly interconnected with the hypothalamus. It was also pointed out that sensory stimulation by way of various intero- and exteroceptive systems evokes rhythmically recurring potentials in certain parts of the limbic cortex that persist for a considerable time after the cessation of the stimulation. Is it possible that the neural perturbations remaining in these structures allow a more ready association of two temporally separated events than is possible in the neocortex where one does not see a comparable phenomenon (41)? If so, it would suggest an explanation of how two temporally separated events might be so related as to impress themselves more readily on the viscera than on the discriminative acts of the skeletal musculature that are presumably dependent on the neocortex.

A number of clinical observations emphasize the importance of the limbic system in memory mechanisms. An inability to recall recent events has been found to be associated with lesions involving any one of the limbic structures forming the neural circuit comprised of the hippocampal formation, mammillary bodies, anterior thalamic nuclei and cingulate gyrus. Sufferers from psychomotor epilepsy, in which the seizure discharge is predisposed to involve limbic structures, have no memory for what they do during their automatisms, some of which may involve a duplication of memorized dexterities and intellectual performance.

Finally, Gantt (21) has made a highly significant observation that has a fundamental bearing on the foregoing considerations. He has found that conditioned cardiac reflexes may persist long after the somatic response conditioned by the same stimulus has been extinguished. In his words, the organism remembers with its heart, but not with specific movements. "Thus the emotional basis for action remains after the external and superficial movements of adaptation have been lost. . . ." He refers to this condition as 'schizokinesis.' This suggests a mechanism that might account for chronic psychosomatic disorders of the cardiovascular system. In the author's laboratory, an attempt was made to discover whether or not the phenomenon of schizokinesis was possibly related to a differential influence of neocortical and limbic systems, respectively, on 'somatic' and 'visceral' functions (41). Hippocampal seizures were induced in cats as a means of bringing about a massive alteration

of function within the limbic system during testing of conditioned cardiac and leg responses. No differential effects were found. Both types of response were abolished during the seizure.

## REFERENCES


1. Bard, P. *Am. J. Physiol.* 84: 490, 1928.
2. Bard, P. *A. Res. Nerv. & Ment. Dis., Proc.* 20: 551, 1940.
3. Bard, P. and V. B. Mountcastle. *A. Res. Nerv. & Ment. Dis., Proc.* 27: 362, 1948.
4. Bard, P. and D. McK. Rioch. *Bull. Johns Hopkins Hosp.* 60: 73, 1937.
5. Beach, F. A. *Psychosom. Med.* 14: 261, 1952.
6. Beattie, J. *Canad. M.A.J.* 26: 400, 1932.
7. Beaumont, W. *Experiments and Observations on the Gastric Juice and the Physiology of Digestion.* Plattsburgh, N. Y.: F. P. Allen, 1833.
8. Bichat, X. *Recherches physiologiques sur la vie et la mort.* Paris: Brosson, Gabon, 1800.
9. Breuer, J. and S. Freud. *Studien über Hysterie.* Leipzig: Deuticke, 1895.
10. Broca, P. *Rev. anthropol.* 1 (sér. 2): 385, 1878.
11. Cannon, W. B. *Bodily Changes in Pain, Hunger, Fear and Rage* (2nd ed.). New York: D. Appleton, 1929.
12. Cobb, S. *Emotions and Clinical Medicine.* New York: Norton, 1950.
13. Cushing, H. *Surg. Gynec. & Obst.* 55: 1, 1932.
14. Dunbar, H. F. *Emotions and Bodily Changes.* New York: Columbia, 1935.
15. Edinger, L. Quoted by Vogt & Vogt (65).
16. Erickson, T. C. *A.M.A. Arch. Neurol. & Psychiat.* 53: 226, 1945.
17. Ferrier, D. *The Functions of the Brain.* New York: Putnam, 1880.
18. French, J. D., R. W. Porter, E. B. Cavanaugh and R. L. Longmire. *A.M.A. Arch. Neurol. & Psychiat.* 72: 267, 1954.
19. Freud, S. *General Introduction to Psychoanalysis,* translated by J. Riviere. New York: Garden City, 1938.
20. Fulton, J. F. *Frontal Lobotomy and Affective Behavior.* New York: Norton, 1951.
21. Gantt, W. H. *Ann. New York Acad. Sc.* 56: 143, 1953.
22. Green, J. D. and A. A. Arduini. *J. Neurophysiol.* 17: 533, 1954.
23. Haterius, H. O. *Cold Spring Harbor Symp. Quant. Biol.* 5: 280, 1937.
24. Hess, W. R. *Das Zwischenhirn.* Basel: Schwabe, 1954.
25. Hess, W. R. and A. E. Meyer. *Helvet. physiol. et pharmacol. acta* 14: 397, 1956.
26. Hunsperger, R. W. *Helvet. physiol. et pharmacol. acta* 14: 70, 1956.
27. Johnston, J. B. *J. Comp. Neurol.* 35: 337, 1923.
28. Kelly, A. H., L. E. Beaton and H. W. Magoun. *J. Neurophysiol.* 9: 181, 1946.
29. Klüver, H. and P. C. Bucy. *A.M.A. Arch. Neurol. & Psychiat.* 42: 979, 1939.
30. Kubie, L. S. In: *Recent Developments in Psychosomatic Medicine,* edited by E. Wittkower and R. Cleghorn. London: Pitman, 1954, chap. 7.
31. Lashley, K. S. *Quart. Rev. Biol.* 24: 28, 1949.
32. Liddell, H. S. In: *Feelings and Emotions,* edited by M. L. Reymert. New York: McGraw-Hill, 1950.
33. MacLean, P. D. *Psychosom. Med.* 11: 338, 1949.
34. MacLean, P. D. *Electroencephalog. & Clin. Neurophysiol.* 4: 407, 1952.
35. MacLean, P. D. In: *Recent Developments in Psychosomatic Medicine,* edited by E. Wittkower and R. Cleghorn. London: Pitman, 1954, chap. 6.
36. MacLean, P. D. *Psychosom. Med.* 17: 355, 1955.
37. MacLean, P. D. *A.M.A. Arch. Neurol. & Psychiat.* 78: 113, 1957.
38. MacLean, P. D. *A.M.A. Arch. Neurol. & Psychiat.* 78: 128, 1957.
39. MacLean, P. D. *Am. J. Med.* 25: 611, 1958.
40. MacLean, P. D. In: *The Central Nervous System and Behavior,* edited by M. A. B. Brazier. New York: Macy, 1959.
41. MacLean, P. D., S. Flanigan, J. P. Flynn, C. Kim and J. R. Stevens. *Yale J. Biol. & Med.* 28: 380, 1955/6.
42. MacLean, P. D., N. H. Horwitz and F. Robinson. *Yale J. Biol. & Med.* 25: 159, 1952.
43. Magoun, H. W. *A. Res. Nerv. & Ment. Dis., Proc.* 30: 480, 1952.
44. Mahl, G. F. *Psychosom. Med.* 14: 182, 1952.
45. Margetts, E. L. In: *Recent Developments in Psychosomatic Medicine,* edited by E. Wittkower and R. Cleghorn. London: Pitman, 1954, chap. 3.
46. Masserman, J. H. *Behavior and Neurosis.* Chicago: Univ. Chicago Press, 1943.
47. McCulloch, W. S. In: *Cerebral Mechanisms in Behavior,* edited by L. A. Jeffress. New York: Wiley, 1951.
48. Mushatt, C. In: *Recent Developments in Psychosomatic Medicine,* edited by E. Wittkower and R. Cleghorn. London: Pitman, 1954, chap. 19.
49. Nauta, W. J. H. *J. Comp. Neurol.* 104: 247, 1956.
50. Olds, J. and P. Milner. *J. Comp. & Physiol. Psychol.* 47: 419, 1954.
51. Papez, J. W. *A.M.A. Arch. Neurol. & Psychiat.* 38: 725, 1937.
52. Pavlov, I. P. *Conditioned Reflexes,* translated by G. V. Anrep. London: Oxford, 1927.
53. Pribram, K. H. and M. Bagshaw. *J. Comp. Neurol.* 99: 347, 1953.
54. Pribram, K. H. and P. D. MacLean. *J. Neurophysiol.* 16: 324, 1953.
55. Ramón y Cajal, S. *Studies on the Cerebral Cortex (Limbic Structures),* translated by Lisbeth Kraft. London: Lloyd-Luke, 1955.
56. Rogers, F. T. *J. Comp. Neurol.* 35: 21, 1922.
57. Rosenblueth, A., N. Wiener and J. Bigelow. *Philos. Sc.* 10: 18, 1943.
58. Sawrey, W. L. and J. D. Weisz. *J. Comp. & Physiol. Psychol.* 49: 269, 1956.
59. Schreiner, L. and A. Kling. *J. Neurophysiol.* 16: 643, 1953.
60. Selye, H. *The Physiology and Pathology of Exposure to Stress.* Montreal: Acta Inc. Med. Publ., 1950.
61. Sheehan, D. *A.M.A. Arch. Neurol. & Psychiat.* 35: 1081, 1936.
62. Smith, W. K. *J. Neurophysiol.* 8: 241, 1945.
63. Spiegel, E. A., H. R. Miller and M. J. Oppenheimer. *J. Neurophysiol.* 3: 538, 1940.

64. Vogt, C. and O. Vogt. *Sitzberger. heidelberg. Akad. Wiss. Math.-naturw. Kl.* 14: 3, 1919.
65. von Bechterew, W. *Die Funktionen der Nervencentra.* Jena: Fischer, 1908–1911.
66. von Economo, C. *Encephalitis Lethargica*, translated by K. O. Newman. London: Oxford, 1931.
67. Ward, A. A., Jr. *J. Neurophysiol.* 11: 13, 1948.
68. Weiss, E. and O. S. English. *Psychosomatic Medicine.* Philadelphia: Saunders, 1943.
69. Wiener, N. *Cybernetics, or Control and Communication in the Animal and the Machine.* New York: Wiley, 1948.
70. Wittkower, E. and R. Cleghorn (editors). *Recent Developments in Psychosomatic Medicine.* London: Pitman, 1954.
71. Wolf, S. G. and H. G. Wolff. *Human Gastric Function.* New York: Oxford, 1943.
72. Zubiran, J. M., A. E. Kark, A. Montalbetti, C. J. L. Morel and L. R. Dragstedt. *A.M.A. Arch. Surg.* 65: 809, 1952.

CHAPTER LXX

# Central nervous system circulation, fluids and barriers—introduction

CARL F. SCHMIDT | *Laboratory of Pharmacology, University of Pennsylvania, Philadelphia, Pennsylvania*

CHAPTER CONTENTS



THE PERSPECTIVE of this section is simple in principle but complex in detail because these are the characteristics of the physiology of the brain. It is simple for the following reasons. First, the essential role of the circulation in the brain is the same as that in any other tissue, viz, to meet the call of a mass of living cells for an exchange of fluids and solutes, a source of energy commensurate with their metabolic requirements and a means for removal of their waste products. Second, the organ is unusually homogenous; the function of most of its various components is the same (viz, the origination or conduction of nerve impulses or both), and the consequences of deranged function are easily recognized. Finally, the blood supply also is unusually homogenous and can be measured in normal and diseased man with quantitative accuracy at least equal to that available for the study of the blood flow in other organs. The last named advantage has been within reach only for the last 15 years, but in that time a mass of information has been obtained which is considered in Chapter LXXI by Kety in this *Handbook* and which provides a better insight into the physiology and pharmacology of the human cerebral circulation than is available for any other organ, excepting perhaps the kidney.

These studies on man have substantiated the concept, gained from earlier work on animals (37, 38), that the cerebral blood vessels possess an intrinsic regulatory capacity activated by chemical products of metabolism (carbon dioxide, acid and other resultants of anoxia), having the effect (perhaps the purpose) of maintaining homeostasis with respect to these agents in cells which are highly vulnerable to departures from their optimal chemical environment because they have sacrificed adaptability for specialization. The animal studies indicated that, of all the common chemical products of metabolism, carbon dioxide is most powerful and most uniform in its effect on cerebral vascular tonus. This conclusion is borne out by the subsequent work on man (23, 25), with the modification that the ability of anoxemia to dilate the human cerebral vessels turns out to be relatively greater than would have been expected from the animal experiments (37). Definitive well-controlled estimations of the effects of acid on the cerebral vasculature of man have not yet been reported.

## CEREBRAL VASCULAR ADJUSTMENTS TO CHEMICAL CHANGES IN THE BLOOD

The fundamental concept remains quite simple: the tonus of the blood vessels supplying a given nerve cell is decreased whenever the arterial $pCO_2$ rises and whenever the arterial $pO_2$ or pH falls. If the metabolic activity of the cell remains constant, the carbon dioxide and acid which it produces then will be removed more rapidly, and the oxygen content of the blood in the adjacent capillaries will fall less than had previously been the case. Thus the brain cells

are protected against the full impact of these blood-borne changes to an extent indicated by a decrease in the corresponding cerebral arteriovenous differences. Opposite changes in the arterial blood produce increases in cerebral vascular tonus, widening of the cerebral arteriovenous differences and attenuation of the concomitant changes within the brain cells.

The extent to which these automatic adjustments of the resistance of the human cerebral vessels to induced alterations in arterial $pCO_2$ and $pO_2$ can compensate is greater than was expected from the animal studies. As noted elsewhere (39), the changes in cerebral venous $pCO_2$ of man during inhalation of carbon dioxide or hyperventilation are about half those observed in the arterial blood. These were only moderate shifts (inhalation of 5 to 7 per cent carbon dioxide and hyperventilation short of overt tetany). Studies of the effects of more marked changes in arterial $pCO_2$ are complicated by the occurrence of unconsciousness and convulsions which will have to be obviated before definitive results can be obtained. There is at present no means of knowing whether the cerebral vascular readjustments to changes in arterial $pCO_2$ progress steadily with the intensity of the stimulus or are limited to a definite (presumably physiological) range. The answer to this question might have interesting implications.

The corresponding observations with decreases and increases of arterial $pO_2$ in man have confirmed the general concept outlined above, but they have also yielded some unexpected food for thought. Mild anoxemia (from inhalation of 10 per cent oxygen in nitrogen) in man decreased cerebral vascular resistance about as much as did inhalation of 5 or 7 per cent carbon dioxide, although its effect on total cerebral blood flow was less because of a simultaneous fall in arterial pressure instead of the rise produced by carbon dioxide (25). Since the arterial and cerebral venous $pCO_2$ both fell because of concomitant hyperventilation, it is clear that the vasodilator influence of anoxia was preponderant over the opposing tendency of hypocapnia. This conclusion is a little surprising because the latter, when induced by aminophylline, apparently overshadows in man (42, 47) the distinct cerebral vasodilator effect which this drug exerts in animals (11). Furthermore, the cerebral vasoconstrictor influence of hypocapnia overcame the vasodilator trend of acid in postconvulsive states in man (19, 26) in experimental acidosis (36) and in patients in diabetic acidosis short of coma (24, 31). In comatose diabetics, however, there was cerebral vasodilatation in spite of even more severe hypocapnia (24, 31). The best explanation at present is that the dilatation in diabetic coma represents a transition from the physiological to the pathological range, in which the normal mechanisms are overcome by the beginning of irreversible changes. If this reasoning is applied to the above-mentioned effects of anoxia, these appear as a manifestation of the general principle that "anoxia not only stops the machine, it wrecks the machinery" (5), and the cerebral vasodilator influence of anoxia becomes pathological rather than physiological. Another observation pointing in this direction is the decreased effectiveness of epinephrine as a circulatory stimulant in the presence of anoxemia (45).

Hypocapnia and norepinephrine are the only agencies that have been shown to be capable of causing distinct cerebral vasoconstriction in man, and, of these, hypocapnia is by far the stronger. This also fits into the simple concept of carbon dioxide as the chief regulator of cerebral vascular tonus. The cerebral vasoconstrictor effect associated with oxygen inhalation in animals (11, 37) also was confirmed in man (25, 30), and during oxygen inhalation under 3.5 atm. pressure it became almost as marked as that elicited by hyperventilation with air (30). This, however, now appears not to be due to the oxygen, but to the concomitant hyperpnea and hypocapnia; when the latter is obviated by addition of carbon dioxide to the inhaled oxygen in amounts appropriate for the maintenance of a constant arterial $pCO_2$, inhalation of oxygen produces no cerebral vasoconstriction in man (46). At the same time the cerebral venous (and presumably tissue) $pO_2$ rises markedly and the convulsant effects of hyperoxia come on much more rapidly than before (29). Thus the hyperventilation induced by oxygen inhalation, particularly under pressures greater than 1 atm., appears as a potent means for protecting the brain cells against the toxicity of excessive oxygen pressures (28)—another manifestation of the homeostatic role of intrinsic adjustments of cerebral vascular tonus in relation to blood-borne changes in the respiratory gases.

### CEREBRAL VASCULAR ADJUSTMENTS TO METABOLIC REQUIREMENTS OF BRAIN CELLS

Here the simple concept derived from experiments on animals has not been substantiated by studies on man. Animal experiments indicated that an increase in the functional activity of the entire brain (such as that produced by pentylenetetrazol or picrotoxin in

convulsant dosage) automatically entailed a decrease in cerebral vascular resistance sufficient to produce a marked increase in total cerebral blood flow (41). A similar increase in blood flow in a localized area (the visual cortex) was also demonstrated when the functional activity of this region was increased by a physiological stimulus, such as illumination of the eye (40). Since arterial pressure fell in the former case and did not change in the latter, an automatic adjustment of cerebral vascular tonus to the metabolic requirements of the tissue was indicated.

The changes in the cerebral vascular tonus of man at the instant of a convulsion have not been studied as yet because the method generally used is not adapted to fluctuations in pulmonary ventilation. Observations have been made in human subjects as soon as possible after the resumption of regular breathing following the convulsions of electroshock (26), pentylenetetrazol (26) and epilepsy (19), but all have shown only a decrease in cerebral blood flow and an increase in cerebral vascular resistance at this time. These results can be attributed to the concomitant hypocapnia and acidosis (from the antecedent muscular activity) and may be regarded as another manifestation of the preponderance of $pCO_2$ over $[H^+]$ when they change in opposite directions. With these assumptions, the findings do not necessarily discredit the original concept, but they certainly do not substantiate it. The question might be answered by experiments on man in whom the muscular movements of convulsant agencies were obviated by curare, decamethonium or succinyl choline, but this rather formidable experiment has not seemed justifiable and a better approach would be to use a method capable of revealing instantaneous changes in cerebral vascular resistance. Localized cerebral vascular adjustments to localized changes in functional activity in the brain also have not been studied in man largely because of lack of a suitable method.

Other observations in man cast even greater doubts on the validity of the simple concept derived from animal experiments. The increased cerebral activity associated with mental arithmetic caused no measurable increase in cerebral blood flow (44) and the onset of sleep was associated with an increase rather than a decrease in this function (31). Since there was no concomitant change in cerebral oxygen consumption, these findings are not compelling evidence; but they indicate at least that the situation is not as simple as the one postulated from the animal experiments. Drugs which depressed cerebral functional activity, such as thiopental (22), alcohol (6) and insulin (26), depressed the cerebral oxygen uptake of man; but the cerebral vascular resistance was decreased, not increased. This discordant finding also may be discounted by attributing it to an inactivation by the drugs of the normally precise intrinsic regulating mechanism of the cerebral vessels. If this is so, the homeostatic mechanisms alluded to above do not operate in anesthetized or comatose man and his brain cells will feel the full impact of changes in the arterial blood gases. Such a suggestion was advanced some years ago to account for the occurrence of vasomotor depression during hyperventilation under anesthesia (37), but the matter has not been studied further.

It is evident that there is at present no direct evidence to substantiate the concept that the blood vessels supplying brain cells of man automatically alter their tonus in relation to changes in the functional or metabolic state of the cells. The speculations in an earlier publication (37) as to the mechanisms by which such adjustments are brought about therefore have lost much of their challenge and have not been pursued further. Recent developments indicating that vasoactive substances such as acetylcholine, serotonin and norepinephrine are liberated by nerve impulses, at least in some parts of the brain, may necessitate reopening of this question (see below).

### ROLE OF VASOMOTOR NERVES IN THE CONTROL OF THE CEREBRAL CIRCULATION

Experiments on cats indicated that the parts of the brain above the tentorium possess a vasoconstrictor innervation via the cervical sympathetic (37) and a vasodilator innervation carried by the great superficial petrosal nerve (8, 16). The pons and medulla showed no signs of the former (37); the latter was not tested here. Experiments in man have revealed no sign of a cerebral vasoconstrictor innervation in the corresponding sympathetic pathways (20, 35); the vasodilator innervation has not been studied. It is perhaps significant that measurements of total cerebral blood flow in the monkey failed to give any evidence of cerebral vasoconstriction on stimulation of the cervical sympathetic nerve (11). This observation indicates that the results in cats were not due entirely to the use of an artificial electrical stimulus that has no physiological equivalent, for the same stimulus had no such effect in the monkey. The similarity of the results in man and monkey may indicate a species difference between these and the cat, an instrumental

artefact in the latter, or a spotty distribution of the sympathetically induced vasoconstriction of such a nature as to leave total cerebral blood flow unchanged while reducing it in certain limited areas.

There is at present no evidence upon which this question can be answered. Cerebral angiospasm is frequently advanced as an explanation for transitory, completely reversible clinical derangements, but the only agency by which a physiologically significant degree of cerebral vasoconstriction has been produced in man is hyperventilation. It is, of course, possible that a usually rudimentary vasoconstrictor innervation can become abnormally active, and that a normally sharply localized neurogenic vasoconstriction may involve parts of the brain not ordinarily affected; but of this there is as yet no evidence.

### INFLUENCE OF NEUROHUMORAL AGENTS

Studies of total cerebral blood flow in monkeys indicated that these vessels can be constricted by epinephrine (and other sympathomimetic drugs) and dilated by acetylcholine and histamine, provided that the drugs were injected into the cerebral arterial stream (11). When they were given systemically, cerebral blood flow passively followed the concomitant changes in arterial pressure. Observations similar to the latter have been made in man with epinephrine (27) and histamine (1). Norepinephrine was not tested in the monkey, but it is the only agent (other than hypocapnia) that has been shown to be able to constrict the cerebral vessels of man (27).

Such findings are interesting in themselves, but they acquire new significance in the light of recent animal studies which indicate a considerable physiological and pharmacological significance for norepinephrine, acetylcholine and 5-hydroxytryptamine (serotonin) as chemical mediators in certain parts of the brain (21). It is noteworthy that these agents are found in highest concentration in the hypothalamic region (21) where the histamine concentration also is highest (13). So far the possible relationship of release of such chemicals to local cerebral vascular adjustments appears not to have been considered. Acetylcholine and histamine are known to be capable of dilating the cerebral vessels of animals when applied locally (15, 17, 48) or injected intra-arterially (40). Norepinephrine and serotonin were not then available, but since epinephrine (a weaker vasoconstrictor than its demethylated congener) was shown to be a cerebral vasoconstrictor when so administered in animals (11, 40), and since norepinephrine is known to be similarly active in man (27), this agent at least should increase cerebral vascular tonus at the site of its liberation. Serotonin has not been studied in this respect, but it is a smooth muscle stimulant in general (12) and it would therefore be expected to act like norepinephrine.

Thus there is a clear possibility of an intrinsic, localized cerebral vascular regulation by means of vasoactive agents liberated from brain cells. The direction and extent of the resulting change in vascular tonus should vary according to the preponderance of vasodilator (acetylcholine, perhaps histamine) or vasoconstrictor influences (norepinephrine, possibly serotonin). All these agents are inactivated by appropriate enzyme systems and therefore would exert only brief effects. A mechanism of this type could explain localized cerebral vasodilatation, such as that in the visual cortex on illumination of the eye (40), without involving a vasodilator innervation or a local accumulation of vasodilator metabolites. The situation would be analogous to that seen in the submaxillary gland on stimulation of the chorda tympani nerve; both increased secretion and vasodilatation here are attributed to liberation of acetylcholine (4). A corresponding reduction in blood flow in other areas by preponderance of vasoconstrictor agents would provide for a redistribution of blood within the brain with little or no change in total blood flow or total arteriovenous oxygen difference. It might also furnish a basis for localized cerebral angiospasms.

### 'TRIGGER ZONES' IN THE BRAIN

In Chapter LXXII of this *Handbook* Davson points out that certain parts of the brain are more permeable than others to blood-borne chemicals. Such regions are the area postrema, the paraphysis, the wall of the optic recess, the eminentia saccularis of the hypophyseal stem, the neurohypophysis and the pineal body. They have in common a lack of neuronal tissue and may be regarded as essentially nonneural parts of the brain.

The physiological significance of this coincidence (practical absence of the usual blood-brain barrier in parts of the brain that lack the usual structural framework of the organ) is at present unknown, but there are a few suggestive pieces of information. The area postrema is well established as a site of chemoreceptors for the medullary vomiting center (7). The

neurohypophysis and the adjacent parts of the hypothalamus are recognized as the site of formation of specific antidiuretic and oxytocic hormones (14). The pineal body has recently been implicated by Altschule (2) as the site of formation of a substance (probably a peptide) which is capable of inducing more nearly normal behavior patterns in psychotic individuals. The writer knows of no corresponding studies of the other nonneural areas listed above.

In the case of the area postrema, the situation appears to be relatively simple; blood-borne foreign chemicals which do not readily pass the blood-brain barrier elsewhere can freely enter this region, combine with appropriate chemoreceptors and thus give rise to nerve impulses which excite the vomiting center. The corresponding relations of the neurohypophysis and the adjacent tissues are less clear, but there is evidence (33) that acetylcholine can trigger the release of the antidiuretic hormone and the same is true of drugs which release histamine (10). The antidiuretic component of the neurohypophyseal secretion, according to recent findings (32), can activate the elaboration or release of adrenocorticotropic hormone by the adenohypophysis. Norepinephrine and epinephrine also have been held to be important activators of the latter mechanism (18) but whether directly or through liberation of neurohypophyseal hormones is at present unknown.

Viewed in this light, the unusually great permeability of these parts of the brain may be of great significance in relation to the rapidly developing concept of liberation of acetylcholine, norepinephrine and serotonin in the hypothalamus (21). The role of histamine remains to be established, but its relatively high concentration in this part of the brain is suggestive. Apart from their possible role in the local control of cerebral vascular tonus (see the preceding section), such small molecule agents appear to be able to act as trigger mechanisms in the liberation of larger, more specific molecules such as vasopressin, oxytocin and adrenocorticotropin. The presently controversial 'antischizophrenic' agent in the pineal body, if eventually proved to play an important role in the alleviation of abnormal mental behavior, may deserve study from the standpoint of possible relations of serotonin and norepinephrine to the physiology and pharmacology of the mind (21). The information available for the area postrema indicates the possibility that more or less specific reflexes may play a role in some of the functions of these nonneural regions. Direct effects of relatively nonspecific small molecule agents on tissues which elaborate more specific peptide or protein hormones may also be considered. The early observations of Cushing (9), indicating that pituitary extract produces strong activation of the parasympathetic centers when injected into the cerebral ventricles, also appear to deserve re-examination in the light of the current concept that the effects of some of the tranquilizing drugs are a manifestation of preponderance of the parasympathetic over the sympathetic centers of the brain (34).

In this connection mention may also be made of another seemingly unrelated recent trend in relation to the central regulation of water and salt balance. Smith (43) has recently presented evidence suggestive of a hypothalamic control of water and salt absorption by the renal tubules as a result of inhibitory impulses arising from 'volume receptors' in the pulmonary veins (or left atrium) and the peripheral arterial tree (or tissue spaces). Baroreceptor reflexes, inhibitory to central vasomotor mechanisms, are known to arise from the pulmonary veins and from many peripheral arteries (3); but they have not previously been brought into relation with a concomitant inhibition of the output of hormones. The agent responsible for regulating the renal tubular reabsorption of water presumably is the antidiuretic hormone of the neurohypophysis. For the corresponding conservation of sodium a 'primitive antinatriuretic hormone' is postulated (43).

Further developments of this interesting idea are to be expected. At present it stands as one more item of evidence of possible—and hitherto unsuspected—relationships among nerve impulses, chemical agents, and the regulation of highly specialized functions in the brain and elsewhere. The peculiar structure and permeability relations of the nonneural parts of the brain seem to indicate a special role for them, but this remains to be proved.

In the preceding discussion it has been assumed that the eventual effects, whether referable to the combination of chemical agents with chemoreceptors in a 'trigger zone,' liberation of chemical mediators by afferent impulses, or alterations in the rate of formation or release of specific peptide or protein hormones, are due to direct intervention of the corresponding agents in the specific metabolic reactions of the cells concerned. It is possible that changes in local vascular tonus, dependent on the nature and concentration of vasoactive substances, also may play a part in such events. At present there is no information either as to the possibility of such occurrences, or the influences (if any) which they might exert on the

normal activities of the systems involved. This much is certain—the present period is a transitional one in this area of physiology, as in many (perhaps all) others. Much has been learned about the cerebral circulation and the exchanges between brain cells and the ambient fluids, but integration of this information into the rapidly changing scene portrayed in the other parts of this volume is barely begun. The introduction of the newer psychotropic drugs has stimulated a re-examination of previously held concepts of the integration of the functions of the brain and has led to a concentration of attention on subcortical areas. Questions of chemical mediation of nerve impulses in these regions have become much more pressing than before. At present the information is more or less amorphous. In the past, effective synthesis of such information has been accelerated or forced by the introduction of new therapeutic agents, or by a determined attempt to explain the effects of agents already in use. This situation now prevails in the area of psychopharmacology, and the above sections illustrate the writer's opinion that appropriate studies, by methods devised or adapted for the purpose, are greatly to be desired.

## REFERENCES


1. Alman, R. W., M. Rosenberg and J. F. Fazekas. *A.M.A. Arch. Neurol. & Psychiat.* 67: 354, 1952.
2. Altschule, M. D. *New England J. Med.* 257: 919, 1957.
3. Aviado, D. M. and C. F. Schmidt. *Physiol. Rev.* 35: 247, 1956.
4. Babkin, B. P., A. Alley and G. W. Stavraky. *Canad. M. A. J.* 26: 582, 1932.
5. Barcroft, J. *Nature, London* 106: 125, 1920.
6. Battey, L. L., A. Heyman and J. L. Patterson. *J.A.M.A.* 152: 6, 1953.
7. Borison, H. L., and S. C. Wang. *Pharmacol. Rev.* 5: 193, 1953.
8. Chorobski, J. and W. Penfield. *A.M.A. Arch. Neurol. & Psychiat.* 28: 1257, 1932.
9. Cushing, H. *Proc. Nat. Acad. Sc. Washington*, 18: 500, 1932.
10. de Bodo, R. C. *J. Pharmacol. & Exper. Therap.* 82: 74, 1944.
11. Dumke, P. R. and C. F. Schmidt. *Am. J. Physiol.* 138: 421, 1943.
12. Ersparmer, V. *Pharmacol. Rev.* 6: 425, 1956.
13. Feldberg, W. *Histamine* (Ciba Foundation Symposium). Boston: Little, 1956, p. 6.
14. Fisher, C., W. P. Ingram and S. W. Ranson. *A.M.A. Arch. Neurol. & Psychiat.* 34: 124, 1935.
15. Forbes, H. W., K. H. Finley and G. I. Nason. *A.M.A. Arch. Neurol. & Psychiat.* 30: 957, 1933.
16. Forbes, H. W., C. F. Schmidt and G. I. Mason. *Am. J. Physiol.* 125: 216, 1939.
17. Forbes, H. W., H. G. Wolff and S. Cobb. *Am. J. Physiol.* 89: 266, 1929.
18. Gerschberg, H., E. G. Fry, J. R. Brobeck and C. N. H. Long. *Yale J. Biol. & Med.* 23: 32, 1950–51.
19. Grant, F. C., E. B. Spitz, H. A. Shenkin, C. F. Schmidt and S. S. Kety. *Tr. Am. Neurol. A.* 72: 82, 1947.
20. Harmel, M. H., J. H. Hafkenschiel, G. M. Austin, C. W. Crumpton and S. S. Kety. *J. Clin. Invest.* 28: 415, 1949.
21. Himwich, H. E. *Science* 127: 59, 1958.
22. Himwich, W. A., E. Hamburger, R. Maresca and H. E. Himwich. *Am. J. Psychiat.* 103: 689, 1947.
23. Kety, S. S. *Am. J. Med.* 8: 205, 1950.
24. Kety, S. S., B. D. Polis, C. S. Nadler and C. F. Schmidt. *J. Clin. Invest.* 27: 500, 1948.
25. Kety, S. S. and C. F. Schmidt. *J. Clin. Invest.* 27: 484, 1948.
26. Kety, S. S., R. B. Woodford, F. A. Freyhan, M. H Harmel, K. E. Appel and C. F. Schmidt. *Am. J. Psychiat.* 104: 765, 1948.
27. King, B. D., L. Sokoloff and R. L. Wechsler. *J. Clin. Invest.* 31: 273, 1952.
28. Lambertsen, C. J. In: *Pharmacology in Medicine* (2nd ed.), edited by V. A. Drill. New York: McGraw-Hill, 1958, p. 815.
29. Lambertsen, C. J., J. H. Ewing, R. H. Kough, R. Gould and M. W. Stroud. *J. Appl. Physiol.* 8: 255, 1955.
30. Lambertsen, C. J., R. H. Kough, D. Y. Cooper, G. L. Emmel, H. H. Loeschcke and C. F. Schmidt. *J. Appl. Physiol.* 5: 471, 1953.
31. Mangold, R., L. Sokoloff, E. Conner, J. Kleinerman, P. G. Therman and S. S. Kety. *J. Clin. Invest.* 34: 1092, 1955.
32. McCann, S. M. *Endocrinology* 60: 664, 1957.
33. Pickford, M. *J. Physiol.* 106: 264, 1947.
34. Plummer, A. J., A. Earl, J. A. Schneider, J. Trapold and W. Barrett. *Ann. New York Acad. Sc.* 59: 8, 1954.
35. Scheinberg, P. *Am. J. Med.* 8: 139, 1950.
36. Schieve, J. A. and W. P. Wilson. *J. Clin. Invest.* 32: 33, 1953.
37. Schmidt, C. F. *Fed. Proc.* 3: 131, 1944.
38. Schmidt, C. F. *The Cerebral Circulation in Health and Disease.* Springfield: Thomas, 1950.
39. Schmidt, C. F. In: *Medical Physiology*, edited by P. Bard. St. Louis: Mosby, 1956, p. 402.
40. Schmidt, C. F. and J. P. Hendrix. *A. Res. Nerv. & Ment. Dis., Proc.* 18: 229, 1937.
41. Schmidt, C. F., S. S. Kety and H. H. Pennes. *Am. J. Physiol.* 143: 33, 1945.
42. Shenkin, H. A. *J. Appl. Physiol.* 3: 465, 1951.
43. Smith, H. W. *Am. J. Med.* 23: 623, 1957.
44. Sokoloff, L., R. Mangold, R. L. Wechsler, C. Kennedy and S. S. Kety. *J. Clin. Invest.* 34: 1101, 1955.
45. Surtshin, A., S. Rodbard and L. N. Katz. *Am. J. Physiol.* 152: 623, 1948.
46. Turner, J., C. J. Lambertsen, S. G. Owen, H. Wendel and H. Chiodi. *Fed. Proc.* 16: 130, 1957.
47. Wechsler, R. L., L. M. Kleiss and S. S. Kety. *J. Clin. Invest.* 29: 28, 1950.
48. Wolff, H. G. *Physiol. Rev.* 16: 545, 1936.

CHAPTER LXXI

# The cerebral circulation

SEYMOUR S. KETY | *National Institute of Mental Health, Bethesda, Maryland*

CHAPTER CONTENTS



THERE IS NO ORGAN, other than the heart itself, more completely dependent upon its supply of blood than is the brain. An interruption of this circulation for only 5 sec. produces remarkable changes in neurological function and consciousness (84), while irreversible damage to the brain results if cerebral ischemia persists for more than a few minutes. Although the brain's great need for oxygen, or some essential component of air, was clearly recognized by Hippocrates, it was not until 1783, more than a century after Harvey had described the circulation of the blood, that serious attention was given to the physiology of the cerebral circulation. At that time, Monro (73), later supported by Kellie (45), elaborated a doctrine that the skull being rigid and its contents incompressible, the blood volume of the brain was fixed and, therefore, so also was its circulation—that there was in fact no variation possible in the flow of blood to this important organ. This concept survived scientific scrutiny for another century until 1896 when Hill (42) summarized his fairly extensive experimental studies in animals, concluding that the cerebral blood flow was, in fact, variable but passively so, being governed entirely by the systemic arterial and venous pressures. A few years earlier, Roy and Sherrington had suggested an intrinsic control of the cerebral circulation on the basis of carbon dioxide concentration, but Hill's concept dominated the field for 25 years (49).

Forbes (25) was among the first to direct attention to the intrinsic control of the cerebral circulation, and recent studies in unanesthetized man have amply confirmed its importance. Wolff, in 1936, wrote an excellent review on the entire field of the cerebral circulation up to that time (111), while the work in human cerebral circulation has been reviewed more recently (48, 64a, 69, 103).

## ANATOMY

The brain of almost all mammalian species may be supplied with blood by means of several major sources, including the internal and external carotids and the vertebrals, although there exist wide variations among the species with respect to the relative importance of these several channels. Even though the internal carotid leads directly to the brain, this vessel in some species is relatively unimportant or even vestigial and it is the external carotid which often carries the larger share of cerebral blood which reaches the brain by way of the *rete mirabile*, a coarse network of anastomoses between branches of the extracerebral and the intracerebral circulation (3). Among the species of special interest, laboratory rodents receive their cerebral blood chiefly by way of the well developed vertebrals, with the internal carotids playing a secondary role. In these species

there is no *rete mirabile* and the external carotid provides no significant source. In the dog and cat the chief supply is from the external carotids by way of a well developed *rete mirabile* and from the vertebrals; the internal carotids are of minor significance in the dog and vestigial in the cat.

The primates, including man, demonstrate the best isolation between the intracranial and extracranial blood supply, with only negligible anastomoses between them, the supply being largely via the internal carotids with the vertebrals contributing significantly. In the rhesus monkey the fractions of total flow provided by these two sources are three quarters and one quarter, respectively (14). For these reasons the more reliable studies on cerebral circulation have usually been performed in primates or in man since studies in lower animals require an extensive surgical exposure of the vessels with ligation of those not involved in the cerebral circulation.

The main arteries supplying the brain communicate with each other in a system of anastomoses, designated the circle of Willis, involving fairly large-sized vessels at the base of the brain. There is evidence, however, that, under normal conditions, little communication occurs between the various arterial sources at the circle of Willis (71) which is not unexpected since the pressure in all of the contributing vessels must be approximately the same. Experiments in lower animals (71) and the experience of many radiologists with cerebral arteriography in man (44) leave little doubt that, for the most part, each cerebral hemisphere is supplied by the carotid on that side, while the structures in the posterior fossa receive their blood supply from the basilar artery. There is evidence that in man the circle of Willis functions in emergencies, for when one internal carotid is ligated, the pressure distal to the ligature is maintained at approximately half its previous value because of the contributions through the circle of Willis (107). In young individuals, ligation of one internal carotid does not cause a reduction in the total circulation to the brain, although such a diminution may occur and be associated with neurological symptoms in elderly individuals where the component vessels of the circle may be sclerotic and unable to dilate (100).

The capillary supply to the brain is rather rich (8, 11), although not nearly as rich as that to other organs such as the heart. In cerebral cortex there is an average of about 1000 capillaries per $mm^2$ of cross-section and in white matter about 300 (12, 15, 112), as compared to more than 5000 capillaries per $mm^2$ in the myocardium. Studies of the capillary structure of brain reveal no evidence of arteriovenous anastomoses (8, 24, 86, 112) such as occur in many other tissues.

In the cerebral venous system the blood flow tends to lose its laterality to some extent (4) since the superior and inferior sagittal sinuses drain blood from both sides of the brain. The inferolateral surfaces of the hemispheres, however, drain unilaterally through the respective lateral sinus to the ipsilateral internal jugular vein, and the superior and inferior petrosal sinuses drain directly into the ipsilateral jugular bulb.

Because of its relevance to methods of measuring cerebral blood flow, the question concerning the validity of sampling a single internal jugular bulb merits some attention (55). The superior sagittal sinus appears to drain the cortex of both cerebral hemispheres, continuing, in most individuals, as the right lateral sinus and right internal jugular vein, while the inferior sagittal sinus, draining the subcortical masses, passes into the left internal jugular. This has suggested to some (43) that in the average man, blood in the right internal jugular may be predominantly of cortical origin while that in the left arises from subcortical regions. A number of additional anatomical considerations, however, militate against that conclusion. The superficial cortical veins at their origin dip into subcortical layers (10) so that these, as well as the superior sagittal sinus which drains them, must contain drainage from both white and gray matter. In at least two thirds of individuals there is a competent confluence of the sinuses (torcular Herophili) (18, 30) in which a reasonable amount of intermixing between the superior, inferior and the occipital sinuses occurs. There are, in addition, certain anastomotic veins which cross from the superior sagittal sinus over the surface of the hemispheres to drain into the lateral sinus on each side, while the inferior surface of the hemispheres together with the cerebellum, pons and medulla drain into each internal jugular by way of the lateral or petrosal sinuses. A large number of studies in man on samplings taken simultaneously from both internal jugulars in the waking state (31, 32, 55, 74, 89, 113) and even under anesthesia (43, 109) have disclosed no systematic preponderance of the right over the left with respect to blood flow or oxygen consumption. Furthermore, individual differences between the two sides were within or close to the experimental error in every series save one (43), suggesting that for most purposes values obtained by sampling one jugular bulb are adequately representative of the brain as a whole. Where the best estimate in an individual case is re-

quired, however, some increase in precision is possible by averaging values obtained from the two sides (74).

Although the blood in one superior jugular bulb represents a satisfactory mixture of the drainage from the various cerebral tissues, it is not completely representative of the drainage from both sides of the brain. Dye injection studies indicate that about two thirds of the blood in each jugular bulb is of ipsilateral origin, only one third having crossed the mid-line (101), further substantiating the advisability of bilateral sampling in studies on localized cerebral disease.

Although there has been some indirect evidence for the appearance of some blood of extracerebral origin in the internal jugular vein (21, 88), the only attempt to quantify this contamination found it to be quite small in each of eight subjects (101). An average of 2.7 per cent of the blood in the superior jugular bulb was found to be derived from extracerebral sources with a range from 0.0 to 6.6 per cent.

## METHODS OF STUDY

A number of methods have been used for the study of the cerebral circulation, both generally and locally in both animals and man. In measuring the total cerebral circulation in animals, perfusion methods have been widely used (9, 14, 29, 94, 97) and have, in fact, yielded the most reliable results when attention was given to certain limiting features (14). It is important, of course, that the perfusion flow which is being measured be directed solely to the brain and that all of the cerebral circulation be included in it. In the rhesus monkey, this is possible because of the rather definite isolation of cerebral blood flow from that of the rest of the head, but in the cat and dog it is necessary to demonstrate that such isolation has indeed been secured. Another lesser problem is the choice of a suitable flow meter, and bubble flow meters, rotameters and Venturi meters have been used as has direct measurement of venous outflow.

The flow of blood in the internal jugular of man has been measured by means of a thermoelectric technique (33), using a heated thermocouple enclosed in a needle, the temperature at the thermocouple being some function of the flow of blood about it. Such a technique is difficult to make quantitative or even reproducible (36) and has, in fact, been used only to indicate roughly the relative changes in blood flow in a single internal jugular. The Stewart principle of dye dilution has been applied with varying degrees of success to the measurement of cerebral blood flow in man (34, 78, 101). Since dye injected into one internal carotid will be only partially mixed with the venous return from the contralateral hemisphere (101), it is necessary to secure samples of blood from both internal jugular veins in order to make satisfactory measurements. A more precise approach to the problem entails the administration of the dye into both internal carotids and the sampling from both internal jugulars in order to obtain an approximation to total blood flow through the brain (78). A modified plethysmographic principle has been applied to the brain of man (20), taking advantage of the rigidity of the craniovertebral shell and the incompressibility of its contents. This technique has yielded results which are less than a third of the values obtained by other methods, indicating that occlusion of the cerebral venous outflow is only partially achieved by compressing both internal jugular veins since appreciable quantities of blood must leak out by way of the spinal venous plexus (4, 36).

The Fick principle has been widely applied to measurement of cerebral circulation, especially in man. If cerebral oxygen consumption is assumed to be constant, then by this principle cerebral blood flow would be inversely proportional to the arteriovenous oxygen difference across the brain. Myerson and his associates (75) made possible the sampling of cerebral venous blood in man, and arterial venous oxygen differences have been obtained under a variety of conditions. The validity of relating these to cerebral blood flow, of course, depends upon the validity of the assumption of unaltered cerebral oxygen consumption which, without its independent measure, can be made only on the basis of an astute guess. Investigators who have used this technique have made a large number of correct guesses (65), although the record is by no means perfect.

The nitrous oxide technique (47, 55) is also based upon the Fick principle and, in addition, upon the premise that the uptake by the brain of an inert gas like nitrous oxide would, in contrast to oxygen, be independent of the metabolism or functional activity of the brain and would depend only upon gross composition. In this method, the integral of the arteriovenous nitrous oxide difference[1] over a 10-min. period

[1] This was obtained in the original description of the nitrous oxide technique by serial simultaneous sampling from the femoral artery and internal jugular vein and by arithmetically integrating the resulting curves (47). One modification of this technique which may simplify the procedure consists in the continuous sampling of the two blood sources, thus automatically integrating them (92). Care must be taken to avoid timing and dead-space errors in the latter procedure (106).

of equilibration is used as the denominator in the Fick equation, while the quantity of the gas taken up by unit weight of brain in the same time is the numerator (47). The latter quantity cannot be determined directly in man. If, however, the time of equilibration with the inert gas is sufficiently long, the nitrous oxide tension in the cerebral venous blood will approximate its mean tension in the brain, and since the brain-blood partition coefficient of the gas is practically unity (51), its mean brain concentration will be close to its concentration in mixed cerebral venous blood. Direct analyses in a series of 16 dogs (51) and indirect studies in man (66, 67) using the $\gamma$-radiation of $Kr^{79}$ have indicated that in the case of the brain such equilibrium has, for practical purposes, been achieved at the end of 10 min. This is in accord with calculations based upon values recently determined for the blood flow in various portions of the brain of the unanesthetized cat (63). It seems hardly necessary to point out that for those organs and conditions where satisfactory equilibrium is not achieved in the time interval under examination, the method cannot be used with validity (85).

The effect of the absorption of gas by cerebrospinal fluid has been shown to introduce a small error in the nitrous oxide technique under normal circumstances (1). This could be considerably increased in conditions such as hydrocephalus or cerebral atrophy.

One of the disadvantages of the nitrous oxide technique is the fact that it is incapable of measuring rapid changes in cerebral blood flow. In order to obtain such information in man, another modification of the Fick principle has been made recently in which a $\gamma$-emitting radioactive gas ($Kr^{79}$) is used instead of nitrous oxide, permitting continuous estimation of its uptake by the brain which, in conjunction with arteriovenous differences, makes possible continuous calculation of cerebral blood flow (66, 67).

Another limitation of the nitrous oxide technique is its applicability only to the brain as a whole, yet the need for information on regional circulation in the brain is an obvious one. This problem has been approached by direct visualization and measurement of superficial vessels of the brain (26, 27), or by the use of heated (76) or cooled (96) thermocouples inserted into the substance of the brain. Neither of these approaches has yet been made quantitative, and techniques depending upon measurement of the thermal conductivity of the living brain are subject to error introduced by metabolic heat and the many temperature gradients within the brain (68).

In recent years, measurements have been made on regional circulation in the brains of animals in various conditions by a technique which depends upon the differential uptake of a radioactive inert gas by the various tissues of the brain (53, 63). This can be shown to depend upon the arterial concentration curve, the solubility of the gas in the particular tissue, blood flow and the diffusion process. In the case of the brain, the diffusion can be shown not to be a limiting factor so that, by measuring the various parameters indicated, cerebral blood flow can be calculated.

## NORMAL VALUES AND PHYSIOLOGICAL VARIATIONS OF CEREBRAL CIRCULATION

In table 1, mean normal values for cerebral blood flow in man are presented as they have been reported by investigators using a number of different techniques. In table 2, mean values for regional blood flow obtained in various areas of the cat brain by means of the radioactive gas technique are summarized.

In man the studies on the over-all cerebral circulation have been quite extensive and the variety of conditions sufficiently great that some generalizations may be made for variation in cerebral blood flow with different physiological states.

A longitudinal study of the changes in cerebral blood flow with age has not yet been undertaken, nor has any one group of investigators systematically studied the entire age span. The reliability of conclusions based upon available data is considerably lessened by individual differences in the criteria of selec-

TABLE 1. *Values for Cerebral Blood Flow in Normal Man Obtained by Different Groups Using Various Modifications of the Inert Gas Technique**

| Sex of Subjects | Age, Yr. | Method | CBF ml/100 gm min. | Ref. |
|---|---|---|---|---|
| Male | 25 | Original $N_2O$ | 54 | (55) |
| Male | 71 | Original $N_2O$ | 58 | (104) |
| Mixed | 6 | $N_2O$ microanalytical | 106 | (46) |
| Male | 25 | $N_2O$ microanalytical | 60 | (46) |
| Male | 25 | $N_2O$ continuous sampling | 65 | (92) |
| Mixed | 37 | $N_2O$ continuous sampling | 58 | (6) |
| Male | 38 | $Kr^{85}$ | 51 | (64) |
| Female | 37 | $Kr^{85}$ | 52 | (64) |

* Each value for cerebral blood flow represents the mean of a series performed on patients of approximately the same age.

TABLE 2. *Mean Values for Blood Flow (ml/gm/min) in Representative Areas of the Brain of the Unanesthetized Cat (63)*

| | Mean | | Mean |
|---|---|---|---|
| Inferior colliculus | 1.80 | Caudate | 1.10 |
| Sensorimotor cortex | 1.38 | Thalamus | 1.03 |
| Auditory cortex | 1.30 | Association cortex | 0.88 |
| Visual cortex | 1.25 | Cerebellar nuclei | 0.87 |
| Medial geniculate | 1.22 | Cerebellar white matter | 0.24 |
| Lateral geniculate | 1.21 | Cerebral white matter | 0.23 |
| Superior colliculus | 1.15 | Spinal cord white matter | 0.14 |

tion, in technique and in procedure. There is no reason to question the carefully controlled finding of a very high rate of flow in the first decade of life, falling around the time of puberty toward the value in the young adult (table 1). Groups who have studied middle-aged and elderly hospitalized patients have usually obtained values suggesting a gradual progressive fall in cerebral circulation from the fourth or fifth decade onward (19, 49, 91, 102). Sokoloff has reported, however, that carefully selected aged volunteers in good mental and physical health have a cerebral blood flow which is not significantly different from that observed in healthy young men (104), indicating that a reduction in this function is not a necessary accompaniment of the aging process.

The effect of temperature upon cerebral circulation has not been completely studied through a wide range in the same species. In man the only studies using high temperatures have been made in patients with central nervous system syphilis where induced temperatures of the order of 106°F were not associated with a significant increase in cerebral blood flow (41). Some studies have been reported on the effects of hypothermia in animals (60, 83). These have indicated a decrease in cerebral circulation to a significant extent, although there is some question whether the circulation is reduced more than is cerebral oxygen consumption.

In normal sleep there does not appear to be any significant decrease in cerebral blood flow (70); there is, in fact, a slight but significant increase. This argues strongly against the concept that sleep is dependent upon the presence of cerebral ischemia.

Whatever cerebral exertion is required in the performance of mental arithmetic, it is not accompanied by significant changes in cerebral blood flow or oxygen consumption (105), although both functions may be significantly increased in certain types of anxiety (48).

## CONTROL OF CEREBRAL CIRCULATION

Although a large number of factors may operate to vary the cerebral circulation, these may all be grouped under one or another of only two important variables: the pressure head, i.e. the difference between the arterial and venous pressures at the level of the brain; and the total resistance or hindrance imposed upon the flow of blood through the vessels of the brain.

### *Arterial Pressure Head*

Recent investigation does not substantiate the earlier belief that cerebral blood flow passively follows changes in arterial blood pressure (42). Studies in intact human beings have strengthened the concept that a normal arterial pressure is zealously maintained by numerous homeostatic mechanisms, such as the carotid sinus reflex and the central control of peripheral vascular tone; and that as long as the mean arterial pressure remains above a critical minimum level, cerebral blood flow is actually regulated intrinsically (95) by changes in cerebrovascular resistance. This is nicely illustrated by a report of the maintenance of normal levels of cerebral blood flow through a markedly reduced cerebral vascular resistance where the arterial pressure had been lowered considerably by high spinal anesthesia (61). Where the arterial pressure falls below a level of 60 or 70 mm Hg, then, of course, serious limitation in the cerebral circulation may result (22). This may be seen in carotid sinus hypersensitivity, in the Stokes-Adams syndrome, in orthostatic hypotension and in surgical shock.

Under most conditions, including even cardiac decompensation (77), the venous pressure constitutes so small a fraction of the arterial pressure that it plays a minor role in determining the total pressure gradient. The venous pressure, however, plays an important role in combating the effects of gravity upon the cerebral circulation. In the erect posture (80) or, more dramatically, during exposure to high centrifugal force (39), the effective arterial pressure at head level may be moderately or severely reduced without a comparable reduction in cerebral blood flow. In one study under centrifugal force, cerebral blood flow appeared to be maintained at normal levels even

though the arterial pressure at head level had fallen to very low values. The explanation for this phenomenon lay in the internal jugular pressure which, influenced by the same hydrostatic forces, had fallen well below atmospheric levels, exerting a siphon-like effect.

*Cerebral Vascular Resistance*

Under normal circumstances of maintained arterial pressure and normally low venous pressure, the regulation of the cerebral circulation resides entirely within the brain itself through the operation of a variety of factors, all of which affect the resistance to the flow of blood. The first of these factors is intracranial pressure, an increase in which has been shown to produce a parallel increase in resistance (57), causing, at intracranial pressures above 500 mm of water, a moderate to severe restriction in cerebral circulation.

The viscosity of the blood is another factor which affects its resistance to flow, although in only two conditions—polycythemia vera and anemia—is the viscosity altered sufficiently to produce marked effects. In the former, a blood flow of less than half the normal values has been observed (48), while in severe anemia the cerebral circulation is significantly increased (40, 82). To what extent changes in local carbon dioxide and oxygen tension brought about by the altered hemoglobin content of the blood operate in association with the viscosity changes in these conditions has not been investigated.

By far the most important single factor, however, is the narrowing or dilatation of cerebral vessels, especially the arterioles; a number of variables operate to alter vascular dimensions, including neurogenic, humoral and organic factors.

*Neurogenic Control*

There is an intrinsic nervous supply to the arteries and arterioles of the brain (81). This appears to originate from the carotid and vertebral plexus, a network of nerve fibers and ganglia which accompany these vessels as they enter the skull. The carotid plexus is supplied by fibers from the superior cervical ganglion and also by a bundle which emerges from the cranium along with the facial nerve, continuing through the greater superficial petrosal. A number of studies in lower animals has demonstrated that stimulation of the cervical sympathetic chain usually produces vasoconstriction in the brain, while stimulation of the greater superficial petrosal or facial nerve produces vasodilatation (27, 76, 81, 96). It has been found, however, that section of both of these supplies does not cause degeneration of the intracerebral vascular nerves, an observation which led to the demonstration of ganglion cells in the carotid plexus (81). There is surprisingly little evidence in favor of a tonic constrictor effect on cerebral vessels, at least that which may be mediated by way of the known sympathetic innervation to the head (38, 96). Studies on the effects of stellate ganglion blockade in man (38, 87), although showing expected evidence of paralysis of the sympathetics to the eye and a dilatation of cutaneous vessels, have failed to show any change in cerebrovascular tone or in cerebral blood flow in the conditions studied.

The possibility of spasm of cerebral vessels, often suggested by certain clinical syndromes and beautifully demonstrated by cerebral embolization in animals (7, 108), has not yet been definitively demonstrated in man. Although arteriographic evidence suggestive of spasm has been obtained (17), such studies are difficult to control rigorously. Most of the clinical evidence for spasm is equally compatible with an explanation on the basis of multiple minor thromboses (23) or transitory systemic hypotension in a critically narrowed vessel (13, 16, 72).

*Humoral Control*

The effect of humoral agents is clearer and more readily demonstrated. Cerebral blood flow shows an excellent correlation with the carbon dioxide tension of arterial blood (54, 56, 65, 79). This has been confirmed in a large number of studies on animals and man using a wide variety of techniques. In man the inhalation of 7 per cent carbon dioxide tends to double the cerebral circulation (56), while hyperventilation produces a marked decrease (54).

The effects of oxygen are quite the reverse of those of carbon dioxide. High concentrations of oxygen exert a mild constricting effect and low oxygen concentrations dilate cerebral vessels, according to studies in normal man (56) and in lower animals. Exposure to several atmospheres of oxygen produces a greater decrease in cerebral blood flow on the basis of a more marked constriction (62). The studies with carbon dioxide and oxygen suggest that these metabolic gases may be the important regulators of cerebral circulation, maintaining an optimal local circulation to meet local metabolic needs. This problem was dealt with in greater detail in the preceding chapter by Schmidt.

*Effects of Drugs*

Most drugs which affect the cerebral circulation do so also by altering cerebrovascular tone. Their effects have been studied by local application, by arterial injection or by intravenous administration in a wide range of dosages in animals and, in man, under conditions of therapeutic dosage and administration. The conclusions have been quite variable if not contradictory because of the tendency to generalize regarding the effects of a drug from results of its administration by one route at a particular concentration in a single species. It is possible to test under appropriate clinical conditions the effects of a number of agents reputed to possess some action on the cerebral circulation. Although in many cases clinical impressions have been quantitatively substantiated, often the results have been somewhat disillusioning.

Reference has been made to the effects of the normal blood gases, oxygen and carbon dioxide. A recent study has suggested that the bicarbonate ion may be an important vasodilator for the brain and has demonstrated a marked increase in cerebral blood flow following the intravenous administration of 3 per cent sodium bicarbonate (93). Although not nearly as effective as carbon dioxide, papaverine administered intravenously has produced a moderate relaxation of cerebral vessels and a modest increase in the cerebral circulation (99).

Contrary to a widespread belief based upon studies in lower animals, the xanthine drugs consistently produce in man a significant cerebral vasoconstriction (99, 110). In convalescent patients the administration of aminophylline intravenously is consistently followed by a marked reduction in cerebral blood flow on the basis of an increase in cerebral vascular resistance. Similar findings have been reported with caffeine.

A number of agents have enjoyed the reputation of being potent vasodilators in the brain, although studies in man with therapeutic dosage have not confirmed their therapeutic efficacy on that basis. Nicotinic acid, while producing facial vasodilatation, has been shown to produce no significant effects upon the cerebral blood flow or cerebral vascular resistance (88). Histamine (2, 99), administered intravenously, although it dilates cerebral vessels, produces at the same time a corresponding decrease in the arterial pressure with the result that the cerebral blood flow is not augmented. When administered intravenously to the point of mild intoxication, ethyl alcohol has produced no significant increase in cerebral blood flow or change in vascular resistance in the brain (5).

Experiments in lower animals have not been consistent with regard to the effects of epinephrine on cerebral vessels (14, 26, 96), and this agent has been listed as a dilator or as a constrictor, depending upon the conditions of the particular experiment. The two studies (59, 98) in man are not in agreement and that may very well be because one group studied the administration of epinephrine intravenously and the other intramuscularly. With intravenous injection at a rate sufficient to elevate the mean arterial pressure by approximately 20 per cent, some interesting differences have been found between the effects of epinephrine and norepinephrine (59). The latter was found to constrict cerebral vessels somewhat more severely than it raised the arterial pressure with the result that there was a slight fall in the cerebral blood flow. Epinephrine itself, on the other hand, neither constricted nor dilated cerebral vessels with the result that the increased arterial pressure produced a significant increase in cerebral blood flow. An excellent and exhaustive review of the effects of drugs on the cerebral circulation has recently been written (103).

## CEREBRAL CIRCULATION IN HUMAN DISEASE

*Cerebral Arteriosclerosis*

Studies upon patients with cerebral arteriosclerosis and senile psychosis (28, 104) have demonstrated a significant decrease in the cerebral circulation and the oxygen consumption of the brain when compared to values found in healthy young men. The restriction of cerebral blood flow is upon the basis of an increased cerebrovascular resistance which was found to be about twice the normal value and which represents a physiological confirmation during life of the well-known sclerotic changes observed in these brains post-mortem.

*Essential Hypertension*

This disease is characterized by an elevation in mean arterial pressure and a corresponding increase in the tone of cerebral vessels with the result that the cerebral circulation remains within normal limits (50). This indicates that the vessels of the brain partake in the generalized vasoconstriction which occurs in this condition. It has also been demonstrated that in essential hypertension, uncomplicated by cerebral arteriosclerosis, the narrowing of the vessels is a functional one which is capable of relaxation should the arterial pressure of such a patient be reduced (22, 37,

52). Thus, the increased cerebral vascular resistance is not the result of permanent structural change. Since it is not released by stellate ganglion blockade (38), it is probably not sympathetic in origin. Although some unidentified vasoconstrictor substance circulating in the blood has often been postulated in this disease, the sudden relaxation in response to a fall in arterial pressure, however achieved, is not easily explained in terms of a circulating humoral agent. The observations generally give most support to the hypothesis that the cerebral vasoconstriction is a compensatory adjustment to the hypertension and may be achieved by the homeostatic effects of the local concentration of carbon dioxide on cerebral vessels.

A large number of diseases have been studied for their relationship to cerebral blood flow. These include epilepsy (35), schizophrenia (58) and multiple sclerosis (90). In none has there been a significant change in cerebral blood flow from the normal or expected value, so that it seems unlikely that a generalized disturbance in cerebral circulation is associated with any of these diseases.

Concepts regarding the cerebral circulation have thus progressed over the past century and a half from one which assumed this function to be fixed, to those which recognized it as variable but entirely at the command of the general circulation, to the most recent ones which appreciate the importance of intrinsic factors in its regulation, making it more responsive to the local needs of the brain and in that way better serving the economy of the body. Much has been learned in recent years concerning the circulation of the brain in its highest state of development—in conscious thinking man. Its fundamental importance to survival and to normal function has been emphasized, but at the same time there has been an opportunity to learn the inadequacies of certain hypotheses which attributed to the cerebral circulation an important role in the more complex and subtle aspects of normal and disturbed mental function. Many problems remain to be elucidated: the nature and mechanism of the intrinsic control, the functions of the nervous supply to cerebral vessels, the question of vascular spasm in the brain, the relationship between regional circulation, metabolism and function in the nervous system. These do not by any means exhaust the list; they are merely an indication of some of the questions to which more satisfactory answers than are now available appear to be within reach.

## REFERENCES


1. Alman, R. W., A. N. Bessman, G. J. Hayes and J. F. Fazekas. *J. Lab. & Clin. Med.* 39: 752, 1952.
2. Alman, R. W., M. Rosenberg and J. F. Fazekas. *A. M. A. Arch. Neurol. & Psychiat.* 67: 354, 1952.
3. Ask-Upmark, E. *Acta psychiat. et neurol.* Suppl. VI, 1935.
4. Batson, O. V. *Fed. Proc.* 3: 139, 1944.
5. Battey, L. L., A. Heyman and J. L. Patterson. *J. A. M. A.* 152: 6, 1953.
6. Bernsmeier, A. and K. Siemons. *Arch. ges. Physiol.* 258: 149, 1953.
7. Broman, T. *Acta Path. et Microbiol. Scand.* Suppl. 42, 1940.
8. Campbell, A. C. P. *A. Res. Nerv. & Ment. Dis., Proc.* 18: 69, 1938.
9. Chute, A. L. and D. H. Smyth. *Quart. J. Exper. Physiol.* 29: 379, 1939.
10. Cobb, S. *Cytology and Cellular Pathology of the Nervous System.* New York: Hoeber, 1932, p. 576.
11. Cobb, S. and J. H. Talbott. *Tr. A. Am. Physicians* 42: 255, 1927.
12. Craigie, E. H. *J. Comp. Neurol.* 31: 429, 1920.
13. Denny-Brown, D. *Med. Clin. N. Amer.* 35: 1457, 1951.
14. Dumke, P. R. and C. F. Schmidt. *Am. J. Physiol.* 138: 421, 1943.
15. Dunning, H. S. and H. G. Wolff. *J. Comp. Neurol.* 67: 433, 1937.
16. Lastgott, H. H. G., G. W. Pickering and C. G. Rob. *Lancet* 2: 994, 1954.
17. Egker, A. and P. A. Riemenschneider. *J. Neurosurg.* 8: 660, 1951.
18. Edwards, E. A. *A.M.A. Arch. Neurol. & Psychiat.* 26: 801, 1931.
19. Fazekas, J. F., R. W. Alman and A. N. Bessman. *Am. J. M. Sc.* 223: 245, 1952.
20. Ferris, E. B. *A.M.A. Arch. Neurol. & Psychiat.* 46: 377, 1941.
21. Ferris, E. B., G. L. Engels, C. D. Stevens and M. Logan. *Am. J. Physiol.* 147: 517, 1946.
22. Finnerty, F. A., L. Witkin and J. F. Fazekas. *J. Clin. Invest.* 33: 1227, 1954.
23. Fisher, M. and D. G. Cameron. *Neurology* 3: 468, 1953.
24. Forbes, H. S. *A. Res. Nerv. & Ment. Dis., Proc.* 18: 92, 1938.
25. Forbes, H. S. *A.M.A. Arch. Neurol & Psychiat.* 43: 804, 1940.
26. Forbes, H. S., K. H. Finley and G. J. Nason. *A.M.A. Arch. Neurol. & Psychiat.* 30: 957, 1933.
27. Forbes, H. S. and H. G. Wolff. *A.M.A. Arch. Neurol. & Psychiat.* 19: 1057, 1928.
28. Freyhan, F. A., R. B. Woodford and S. S. Kety. *J. Nerv. & Ment. Dis.* 113: 449, 1951.
29. Geiger, A. and J. Magnes. *Am. J. Physiol.* 149: 517, 1947.
30. Gibbs, E. L. and F. A. Gibbs. *Anat. Rec.* 59: 419, 1934.
31. Gibbs, E. L., W. G. Lennox and F. A. Gibbs. *Am. J. Psychiat.* 102: 184, 1945.

32. Gibbs, E. L., W. G. Lennox, L. F. Nims and F. A. Gibbs. *J. Biol. Chem.* 144: 325, 1942.
33. Gibbs, F. A. *Proc. Soc. Exper. Biol. & Med.* 31: 141, 1933.
34. Gibbs, F. A., H. Maxwell and E. L. Gibbs. *A.M.A. Arch. Neurol. & Psychiat.* 57: 137, 1947.
35. Grant, F. C., E. B. Spitz, H. A. Shenkin, C. F. Schmidt and S. S. Kety. *Tr. Am. Neurol. A.* 72: 82, 1947.
36. Gregg, D. E. and R. E. Shipley. *Fed. Proc.* 3: 144, 1944.
37. Hafkenschiel, J. H. and C. K. Friedland. *J. Clin. Invest.* 32: 655, 1953.
38. Harmel, M. H., J. H. Hafkenschiel, G. M. Austin, C. W. Crumpton and S. S. Kety. *J. Clin. Invest.* 28: 415, 1949.
39. Henry, J. P., O. H. Gauer, S. S. Kety and K. Kramer. *J. Clin. Invest.* 30: 292, 1951.
40. Heyman, A., J. L. Patterson and T. W. Duke. *J. Clin. Invest.* 31: 824, 1952.
41. Heyman, A., J. L. Patterson and F. T. Nichols. *J. Clin. Invest.* 29: 1335, 1950.
42. Hill, L. *The Physiology and Pathology of the Cerebral Circulation: An Experimental Research.* London: Churchill, 1896.
43. Himwich, W. A., E. Homburger, R. Maresca and H. E. Himwich. *Am. J. Psychiat.* 103: 689, 1947.
44. Hodes, P. J., C. R. Perryman and R. H. Chamberlain. *Am. J. Roentgenol.* 58: 543, 1947.
45. Kellie, G. *Tr. Med.-Chir. Soc. Edinburgh* 1: 84, 123, 1824. [Cited by Hill (42).]
46. Kennedy, C. and L. Sokoloff. *J. Clin. Invest.* 36: 1130, 1957.
47. Kety, S. S. *Methods in Medical Research.* Chicago: Yr. Bk. Pub., 1948, Vol. I, p. 204.
48. Kety, S. S. *Am. J. Med.* 8: 205, 1950.
49. Kety, S. S. In: *Basic Concepts in Cardiovascular Function*, edited by A. P. Fishman and D. W. Richards. London: Oxford. In press.
50. Kety, S. S., J. H. Hafkenschiel, W. A. Jeffers, I. H. Leopold and H. A. Shenkin. *J. Clin. Invest.* 27: 511, 1948.
51. Kety, S. S., M. H. Harmel, H. T. Broomell and C. B. Rhode. *J. Biol. Chem.* 173: 487, 1948.
52. Kety, S. S., B. D. King, S. M. Horvath, W. A. Jeffers and J. H. Hafkenschiel. *J. Clin. Invest.* 29: 402, 1950.
53. Kety, S. S., W. M. Landau, W. H. Freygang, L. P. Rowland and L. Sokoloff. *Fed. Proc.* 14: 85, 1955.
54. Kety, S. S. and C. F. Schmidt. *J. Clin. Invest.* 25: 107, 1946.
55. Kety, S. S. and C. F. Schmidt. *J. Clin. Invest.* 27: 476, 1948.
56. Kety, S. S. and C. F. Schmidt. *J. Clin. Invest.* 27: 484, 1948.
57. Kety, S. S., H. A. Shenkin and C. F. Schmidt. *J. Clin. Invest.* 27: 493, 1948.
58. Kety, S. S., R. B. Woodford, M. H. Harmel, F. A. Freyhan, K. E. Appel and C. F. Schmidt. *Am. J. Psychiat.* 104: 765, 1948.
59. King, B. D., L. Sokoloff and R. L. Wechsler. *J. Clin. Invest.* 31: 273, 1952.
60. Kleinerman, J. and A. L. Hopkins. *Fed. Proc.* 14: 410, 1955.
61. Kleinerman, J., S. M. Sancetta, R. B. Lynn, R. Stahl and D. B. Hackel. *J. Lab. & Clin. Med.* 40: 819, 1952.
62. Lambertsen, C. J., R. H. Kough, D. Y. Cooper, G. L. Emmel, H. H. Loeschcke and C. F. Schmidt. *J. Appl. Physiol.* 5: 471, 1953.
63. Landau, W. M., W. H. Freygang, L. P. Rowland, L. Sokoloff and S. S. Kety. *Tr. Am. Neurol. A.* 80: 125, 1955.
64. Lassen, N. A. and O. Munck. *Acta physiol. scandinav.* 33: 30, 1955.
64a. Lassen, N. A. *Physiol. Rev.* 39: 183, 1959.
65. Lennox, W. G. and E. L. Gibbs. *J. Clin. Invest.* 11: 1155, 1932.
66. Lewis, B. M., L. Sokoloff and S. S. Kety. *Am. J. Physiol.* 183: 638, 1955.
67. Lewis, B. M., L. Sokoloff, W. B. Wentz, R. L. Wechsler and S. S. Kety. *Fed. Proc.* 14: 92, 1955.
68. Linzell, J. L. *J. Physiol.* 121: 390, 1953.
69. Mangold, R. *Schweiz. med. Wchnschr.* 84: 237, 1954.
70. Mangold, R., L. Sokoloff, E. Conner, J. Kleinerman, P. G. Therman and S. S. Kety. *J. Clin. Invest.* 34: 1092, 1955.
71. McDonald, D. A. and J. M. Potter. *J. Physiol.* 114: 356, 1951.
72. Millikan, C., S. S. Kety, C. M. Fisher, I. H. Page, A. Sahs and A. S. Rose. *Neurology* 6: 580, 1956.
73. Monro, A. *Observations on the Structure and Function of the Nervous System.* Edinburgh: Creech, 1783. [Cited by Hill (42).]
74. Munck, O. and N. A. Lassen. *Circulation Res.* 5: 163, 1957.
75. Myerson, A., R. D. Halloran and H. L. Hirsch. *A.M.A. Arch. Neurol. & Psychiat.* 17: 807, 1927.
76. Norcross, N. C. *A.M.A. Arch. Neurol. & Psychiat.* 40: 291, 1938.
77. Novack, P., B. Goluboff, L. Bortin, A. Soffe and H. A. Shenkin. *Circulation* 7: 724, 1953.
78. Nylin, G. and H. Blömer. *Circulation Res.* 3: 79, 1955.
79. Patterson, J. L., A. Heyman, L. L. Battey and R. W. Ferguson. *J. Clin. Invest.* 34: 1857, 1955.
80. Patterson, J. L. and J. V. Warren. *J. Clin. Invest.* 31: 653, 1952.
81. Penfield, W. *A.M.A. Arch. Neurol. & Psychiat.* 27: 30, 1932.
82. Robin, E. C. and F. H. Gardner. *J. Clin. Invest.* 32: 598, 1953.
83. Rosomoff, H. L. and D. A. Holaday. *Am. J. Physiol.* 179: 85, 1954.
84. Rossen, R., H. Kabat and J. P. Anderson. *A.M.A. Arch. Neurol. & Psychiat.* 50: 510, 1943.
85. Sapirstein, L. A. and E. Ogden. *Circulation Res.* 4: 245, 1956.
86. Scharrer, E. *Anat. Rec.* 78: 173, 1940.
87. Scheinberg, P. *Am. J. Med.* 8: 139, 1950.
88. Scheinberg, P. *Circulation* 1: 1148, 1950.
89. Scheinberg P. *Proc. Soc. Exper. Biol. & Med.* 74: 575, 1950.
90. Scheinberg, P., L. I. Blackburn, S. C. Kaim and C. A. Stenger. *A.M.A. Arch. Neurol. & Psychiat.* 70: 260, 1953.
91. Scheinberg, P., L. I. Blackburn, M. Rich and M. Saslaw. *A.M.A. Arch. Neurol. & Psychiat.* 70: 77, 1953.
92. Scheinberg, P. and E. A. Stead. *J. Clin. Invest.* 28: 1163, 1949.
93. Schieve, J. F. and W. P. Wilson. *J. Clin. Invest.* 32: 33, 1953.

94. SCHMIDT, C. F. *Am. J. Physiol.* 84: 202, 1928.
95. SCHMIDT, C. F. *Fed. Proc.* 3: 131, 1944.
96. SCHMIDT, C. F. AND J. P. HENDRIX. *A. Res. Nerv. & Ment. Dis., Proc.* 18: 229, 1937.
97. SCHMIDT, C. F., S. S. KETY AND H. H. PENNES. *Am. J. Physiol.* 143: 33, 1945.
98. SENSENBACH, W., L. MADISON AND L. OCHS. *J. Clin. Invest.* 32: 226, 1953.
99. SHENKIN, H. A. *J. Appl. Physiol.* 3: 465, 1951.
100. SHENKIN, H. A., F. CABIESES, G. VAN DEN NOORDT, P. SAYERS AND R. COPPERMAN. *J. Neurosurg.* 8: 38, 1951.
101. SHENKIN, H. A., M. H. HARMEL AND S. S. KETY. *A.M.A. Arch. Neurol. & Psychiat.* 60: 240, 1948.
102. SHENKIN, H. A., P. NOVAK, B. GOLUBOFF, A. M. SOFFE AND L. BORTIN. *J. Clin. Invest.* 32: 459, 1953.
103. SOKOLOFF, L. *Pharmacol. Rev.* 11: 1, 1959.
104. SOKOLOFF, L. *Proc. Conference on the Process of Aging in the Nervous System.* Springfield: Thomas., 1959.
105. SOKOLOFF, L., R. MANGOLD, R. L. WECHSLER, C. KENNEDY AND S. S. KETY. *J. Clin. Invest.* 34: 1101, 1955.
106. STROUD, W., C. J. LAMBERTSEN, H WENDEL AND M. DEB. DALY. *Fed. Proc.* 13: 147, 1954.
107. SWEET, W. H. AND H. S. BENNETT. *J. Neurosurg.* 5: 178, 1948.
108. VILLARET, M. AND R. CACHERA. *Les Embolies Cérébrales: Études de Pathologie Expérimentale sur les Embolies Solide et Gazeuse du Cerveau.* Paris: Masson, 1939.
109. WECHSLER, R. L., R. D. DRIPPS AND S. S. KETY. *Anesthesiology* 12: 308, 1951.
110. WECHSLER, R. L., L. M. KLEISS AND S. S. KETY. *J. Clin. Invest.* 29: 28, 1950.
111. WOLFF, H. G. *Physiol. Rev.* 16: 545, 1936.
112. WOLFF, H. G. *A. Res. Nerv. & Ment. Dis., Proc.* 18: 29, 1938.
113. YORK, G. E., E. HOMBURGER AND H. E. HIMWICH. *A.M.A. Arch. Neurol. & Psychiat.* 55: 578, 1946.

CHAPTER LXXII

# Intracranial and intraocular fluids

HUGH DAVSON | *Department of Physiology, University College, London, England*

CHAPTER CONTENTS



THE CENTRAL NERVOUS SYSTEM develops from a fluid-filled and fluid-surrounded neural tube. In spite of the varied development of the different parts during embryonic and fetal growth, the adult central nervous system retains this essential feature, the internal cavity having become the ventricles and spinal canal while the enveloping fluid-filled space has become the subarachnoid space. The eye is an outgrowth of the central nervous system and it, too, is filled with fluid—the aqueous humor and the vitreous body, the latter being essentially a dilute aqueous gel, a state of matter best characterized as intermediate between the solid and the liquid. The cerebrospinal and ocular fluids are thus specialized cavity-filling fluids; the one acts as a cushion for the central nervous system while the aqueous humor and vitreous body constitute a part of the refracting media of the visual apparatus and by virtue of their pressure—the intraocular pressure—maintain a degree of rigidity in the system that preserves the corneal curvature. On these mechanical grounds it would not be surprising to find that the physiology of the two fluids had much in common. There is some reason to believe, however, that besides fulfilling these purely mechanical roles, the two fluids are also concerned with the nutrition of the tissues with which they come in close relationship. In the eye this is certainly true, since the lens is a living structure, constituted of a tightly packed mass of transparent fibrous cells, and, being avascular, its prime, if not its sole, source of nutrition is the aqueous humor; to a lesser extent, this fluid is also concerned in the nutrition of the nervous tissue of the eye—the retina. The extent to which the cerebrospinal fluid acts as a nutrient medium for the parenchyma of the central nervous system is still a matter of conjecture, and the problem of the relationship between the cerebrospinal fluid and the nervous tissue is one that will occupy us in this chapter and in Chapter LXXVIII by Tschirgi.

## ANATOMICAL ASPECTS

### *Cerebrospinal System*

The ventricles are illustrated in figure 1; the two lateral ventricles connect, by the interventricular

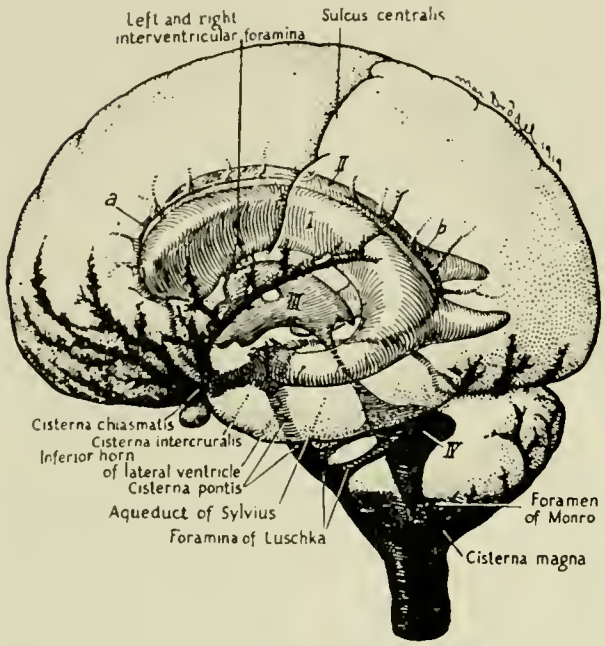



FIG. 1. Ventricles and cisterns of the human brain. [From Clara (45).]

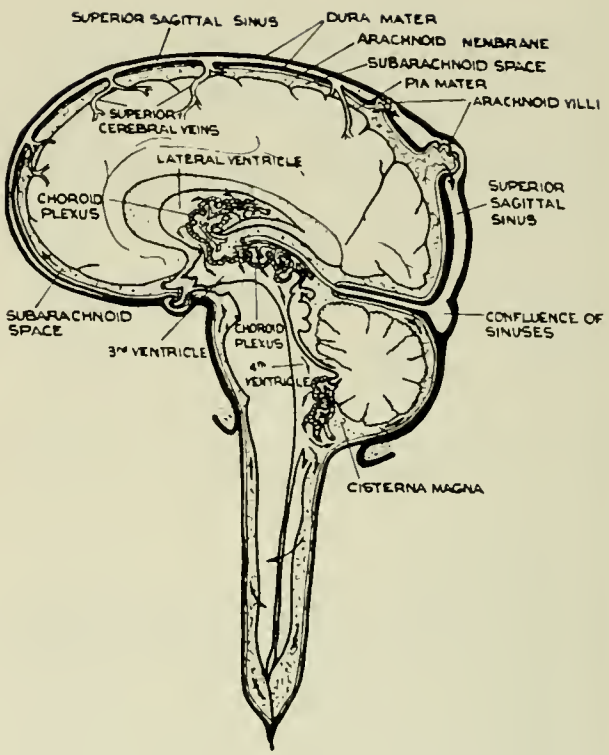



FIG. 2. Ventricles and subarachnoid space [From Rasmussen (182).]

foramina (of Monro), with the third ventricle which connects, by way of the cerebral aqueduct (of Sylvius), with the fourth ventricle on the posterior aspect of the medulla. The subarachnoid space is the space between the arachnoid membrane and the pia; thus, the pia invests the surface of the brain and cord closely, while the arachnoid remains closely apposed to the dura and thus follows the contours of the bony covering. As a result, quite large spaces occur between the two leptomeninges (fig. 2); these are traversed by the arachnoid trabeculae—connective tissue filaments continuous with the arachnoid membrane and, like this, covered with a single layer of mesothelial cells. Since the outer surface of the pia is also covered with a similar mesothelial layer, the fluid in the subarachnoid space is completely enclosed by a mesothelial lining. In certain regions, the subarachnoid spaces are very large, in which case they are called cisterns: for example, the cerebellomedullary cistern or cisterna magna, the cisterna basalis, cisterna ambiens and so on. In man, the fourth ventricle is connected with the subarachnoid space of the cisterna magna by three foramina—a medial opening in the roof of the ventricle, the medial foramen (of Magendie) and the two lateral foramina (of Luschka) leading out of the lateral recesses. In animals below the anthropoid apes the foramen of Magendie is absent (36) so that communication between the ventricles and the subarachnoid space is entirely by way of the foramina of Luschka.[1]

The study of the mode of formation and circulation of the cerebrospinal fluid resolves itself ultimately into a study of the relationship of the fluid with the blood vascular system, and we may profitably dwell in some detail on the anatomical aspects of this relationship. The fluid in the ventricles is separated from the surrounding neuroglial and nervous tissue by a single layer of ependymal cells. In specialized regions this ependyma comes into close relationship with the pia to form the choroid plexuses which are essentially outpouchings of highly vascularized pia protruding into the ventricles and covered on their inner aspect by the layer of ependyma. The ependymal cells covering the plexus, however, become sharply differentiated from their neighbors, being more columnar and losing the long processes that are characteristic of ependymal cells proper;

[1] The foramen of Magendie in man has been described as a post-mortem artefact. According to Barr (20) it is very variable in size. In the majority of cases it is about 16 mm² in area, but it may be so large as to obliterate the roof of the fourth ventricle. In a few cases it may be absent. In 20 per cent of apparently normal individuals Alexander (2) found the foramina of Luschka absent.

they have become, in effect, the choroidal epithelium.[2] On cross-section, therefore, the choroid plexus appears as a fold of epithelium with a core of highly vascularized connective tissue (fig. 3), the epithelium being modified ependyma and the connective tissue, modified pia. The choroid plexuses were early considered to be the regions where the cerebrospinal fluid was elaborated, and this opinion has prevailed to this day, although views still differ as to the existence and the importance of other loci of formation. Early evidence adduced in favor of the choroid plexuses as the sites of formation of the fluid, namely the effects of intravenous injections of drugs such as pilocarpine and of extracts of various glands including the choroid plexuses themselves (73, 157, 171, 217, 237) on the histological appearance of the choroidal epithelium, or on the apparent rate of formation of the fluid, is probably invalid [see, for example, Becht (22)], and it is very questionable whether the epithelial cells do really contain secretory granules (128). The main reason for attributing to the choroid plexuses the role of formation of the fluid rests on the classical studies of Dandy & Blackfan (56) and Frazier & Peet (91) who produced an experimental hydrocephalus in dogs by plugging the aqueduct of Sylvius. If the choroid plexus of one lateral ventricle was removed, and both foramina of Monro blocked, one ventricle dilated while the other collapsed (55).

If the choroid plexuses are the sites of formation of the fluid, and if the latter is being formed continuously—as the pathological phenomenon of hydrocephalus would suggest—we must seek a region in which the fluid is returned to the blood. Key & Retzius (130), by injecting colored gelatin solutions into the subarachnoid space of cadavers, showed that the Pacchionian bodies—large wart-like outgrowths of the arachnoid protruding into the lumina of the dural sinuses—were sites at which the colored material escaped into the vascular system; and more recent work of Weed (233, 235) and of Scholz & Ralston (202), in which the Prussian blue reagents were shown to pass out of the subarachnoid space into the dural sinuses, has confirmed this view, with the difference, however, that the drainage occurs principally by way of microscopic arachnoid villi which are delicate web-like structures continuing the arachnoid membrane into the dura in immediate relationship with a sinus (fig. 4). The villus is capped with a mesothelial covering of arachnoid cells so that the cerebrospinal fluid is separated from the blood in the sinus by this layer and also by the endothelium of the sinus itself. The fluid must therefore filter through these layers.[3]

So far, then, we may picture the cerebrospinal mechanics as the continuous formation of fluid, derived from the blood in the choroid plexuses and associated with a flow out of the ventricles into the subarachnoid space where it passes over the surface of the brain to pass back into the blood in the dural sinuses.[4] It is possible that this picture is too simple; for example, it has been argued that a significant pathway for drainage from the subarachnoid space is by way of the cranial and spinal nerve sheaths [see, for example, Brierley and Field (40, 41)] whence the fluid finds its way into the lymphatics of the epidural tissue (the meninges and brain having no lymphatic system). While it is certainly true that colored solutions pass fairly rapidly from the cranial subarachnoid space along the sheaths of the optic, olfactory and acoustic nerves, the evidence for a flow along the other cranial, and the spinal, nerves is not very striking. Moreover, the studies of Courtice & Simmonds (51), who actually collected lymph after subarachnoid injections, have shown that drainage by this roundabout route is at most only subsidiary, the main escape being a direct one into the blood. A passage of fluid down the so-called Virchow-Robin perivascular spaces[5] has also been postulated by

[2] Strictly speaking, the choroid plexus, as defined by the histologist, consists only of the highly vascularized pia; this, and the closely apposed choroidal epithelium, or lamina epithelialis, make up the tela choroidea.

[3] The Pacchionian bodies are absent in the newborn human and in all the lower animals. It was for this reason that Key & Retzius' demonstration of a flow from the subarachnoid to the dural sinuses was largely ignored. Clark (46) has described the detailed histology of these bodies; they are essentially enlargements of the arachnoid villi, and they occur in all human brains and are not to be regarded as pathological.

[4] The subject of the general direction of flow has been investigated repeatedly by injecting colored particulate matter into the ventricles or subarachnoid space and subsequently inspecting the surface of the brain. [See, for example, Weed (233), Riser (184), Bedford (28), Solomon *et al.* (210) and Sachs *et al.* (194). It is generally agreed that flow from the cisterna magna is mainly by way of the basal cisterna—cisterna basalis, cisterna ambiens, etc. Thence it flows upward over the cerebral and cerebellar convexities. Mixing with the fluid in the spinal subarachnoid space is slow and probably dependent on reflex movements consequent on sudden changes in posture, coughing and so on.

[5] The evidence bearing on the existence of the various spaces—Virchow-Robin, His, Held, etc.—has been well summarized by Woollam & Millen (255). Other useful papers on this subject are those of Patek (169) and Woollam & Millen (256).

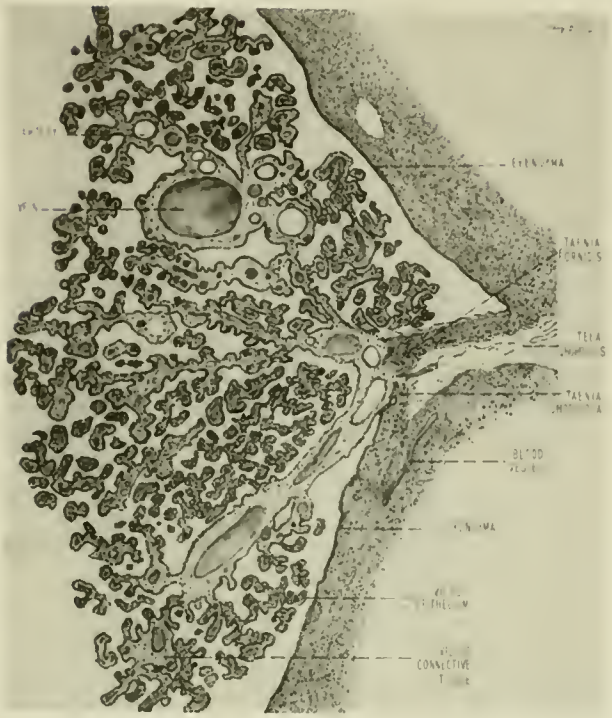


FIG. 3. Choroid plexus. [From Clara (45).]

Mott (162); the large vessels passing from the pia-arachnoid into the nervous tissue carry with them a sheath of pia-arachnoid and there is no doubt that cerebrospinal fluid may, under appropriate conditions, pass from the subarachnoid space proper along the perivascular sheaths which may be regarded as prolongations of the subarachnoid space. If these sheaths were to act as channels carrying cerebrospinal fluid away, they would have to continue as far as the capillaries, and the pressure in these capillaries would have to be low enough to permit the absorption of the fluid. Alternatively, it has been suggested that at least a part of the cerebrospinal fluid is formed by the capillaries of the nervous tissue whence it passes to the surface of the brain up the Virchow-Robin spaces (233). These propositions need not concern us seriously here; at best they may be regarded as subsidiary mechanisms, either of formation or of drainage, and the evidence adduced in their favor, based as it is largely on the fate of injected particulate matter, is equivocal, to say the least.

The pia, it will be recalled, is a connective tissue membrane, lined with mesothelium, that invests the surface of the brain and cord; the great majority of the large arteries and veins supplying the nervous tissue run in the pia before plunging into the parenchyma. It might be considered that in this tissue there would be considerable possibilities of exchanges between the blood and the cerebrospinal fluid. Such exchanges, to be of any quantitative significance, would have to take place across a capillary bed, yet it is by no means certain that the pia has such a capillary bed,[6] so that this region of exchange between blood and fluid is of questionable significance. As we shall see, however, physiological experiments indicate quite unequivocally that exchanges of material between blood and the cerebrospinal fluid, apart from those in the choroid plexuses, do take place and may be of greater significance than those taking place in the plexuses. We must assume, therefore, either that these exchanges occur across the pial vessels or, more probably, from the capillaries of the nervous tissue and thence by diffusion around and through the cells of the parenchyma, up to the subarachnoid space.

*Ocular System*

The aqueous humor occupies the anterior and posterior chambers of the eye (fig. 5); by the posterior chamber is meant the very small space bounded by the posterior surface of the iris, the lens and the vitreous body. The remainder of the cavity of the globe is occupied by the last two mentioned structures, the vitreous body being, as mentioned earlier, a dilute gel built up on a scaffolding of a collagen-like protein and the mucopolysaccharide, hyaluronic acid; since its water content is some 98 per cent or more, it may be considered as a liquid from the point of view of the diffusion of dissolved material within it while its rigidity probably precludes the existence of any significant flow of fluid through it. Functionally, the eye may be regarded as being made up of three coats: an outer protective one, consisting of the sclera and transparent cornea; a middle vascular layer, made up of the choroid, posteriorly, which is continued forward as the ciliary body and the iris; and an innermost layer, the retina, continued forward as the ciliary epithelium and the posterior epithelium of the iris. Figure 6 illustrates the general scheme of vascularization of the human eyeball.

[6] Weed stated in one of his papers that he had never seen a capillary in the pia. On the other hand, Forbes & Cobb (88) in their description of the pial vessels as seen through a cranial window certainly mention capillaries. Schaltenbrand & Putnam (196) observed clouds of fluorescein leaving the pial vessels after an intravenous injection of this dyestuff.

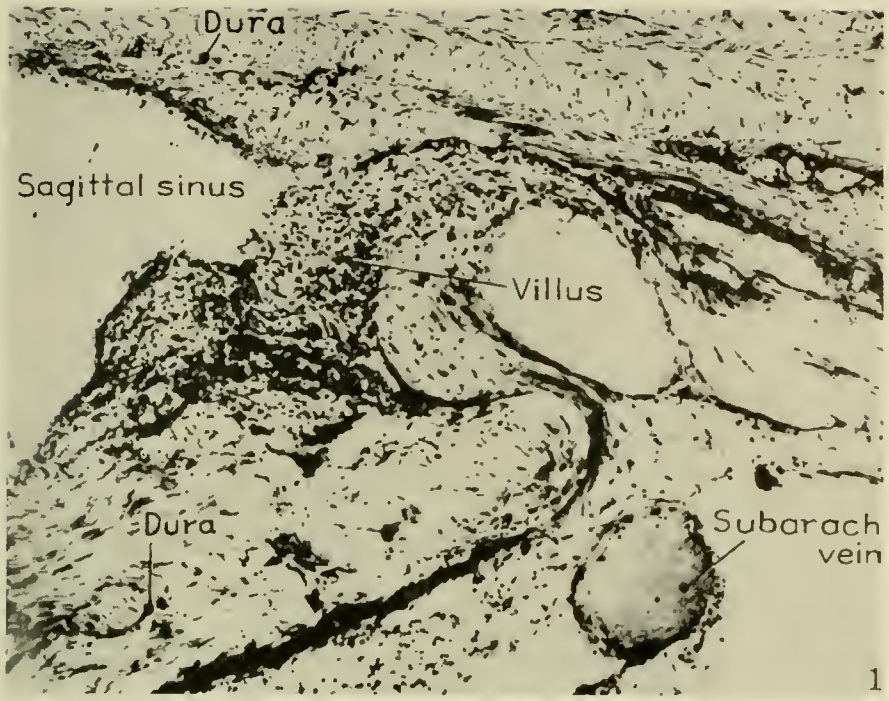



FIG. 4. An arachnoid villus which has invaded the dura and protrudes into the sagittal sinus. The villus may be seen as an outgrowth of the loose cellular tissue of the arachnoid membrane. [From Scholz & Ralston (202).]

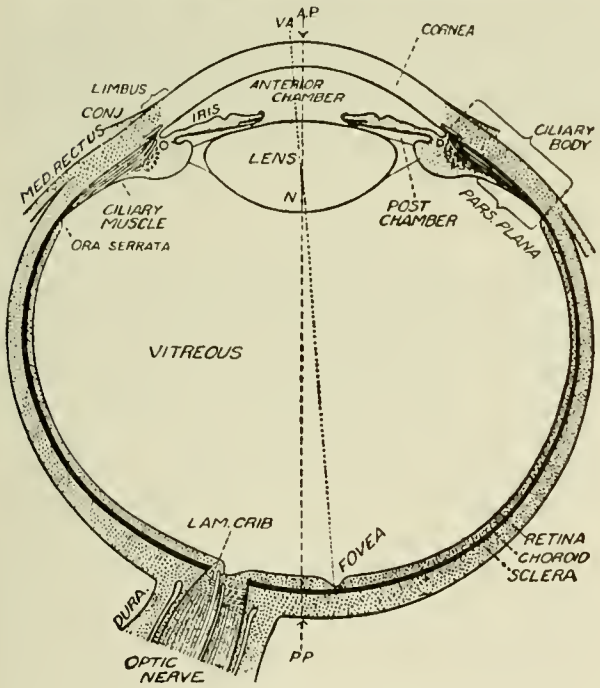



FIG. 5. Anteroposterior section of the human eye. [From Wolff (253).]

The circulation is a dual one; the retinal circulation is mediated by the central artery and vein of the retina which enter the globe in company with the optic nerve; the artery ramifies on the surface of the retina and finally sends capillaries into the inner nervous layers of this tissue while the uveal circulation, mediated by the ciliary arteries, and the anterior ciliary and vortex veins, enters and leaves the globe independently of the optic nerve. The long posterior and anterior ciliary arteries anastomose to form an arterial circle in the ciliary body—the greater circle of the iris. The ramifications of this uveal system constitute the middle vascular coat of the eye; posteriorly, the capillary network derived from the ciliary arteries is called the choriocapillaris and constitutes the nutritional pathway for the outer layers of the retina. Exchanges between blood and vitreous body will clearly take place both from the choriocapillaris and from the capillary networks derived from the retinal artery. More anteriorly, the ramifications of the uveal system give rise to the capillary supplies of the ciliary body and the iris. The venous return from the choroid, the iris and the ciliary processes is by way of four large vortex veins, while the anterior ciliary veins drain the blood from the ciliary muscle and from the series of plexuses in the neighborhood of the cornea (p. 1766).

The structure of immediate concern is the ciliary body; essentially it is made up of the ciliary muscle, concerned with accommodation, and some 80 ciliary processes (fig. 7) projecting into the posterior chamber; each process is supplied by an arterial branch from the major circle of the iris which ramifies in the process into a tangle of capillaries reminiscent of

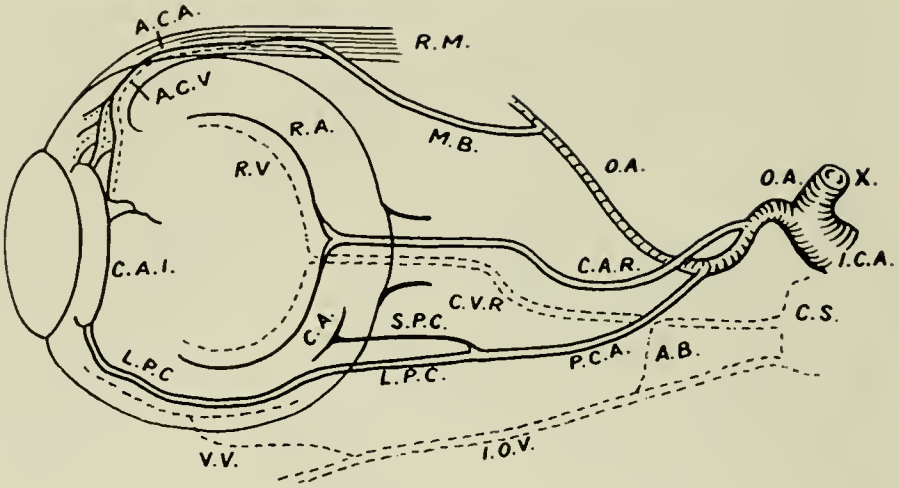



FIG. 6. The circulation of the human eye. *O.A.*, ophthalmic artery; *M.B.*, muscular branch; *A.C.A.*, anterior ciliary artery; *S.P.C.*, short posterior ciliary artery; *P.C.A.*, posterior ciliary artery; *C.A.R.*, central artery of the retina; *R.A.*, retinal artery; *V.V.*, vortex vein; *I.O.V.*, inferior orbital vein; *A.B.*, anastomosing branch; *C.S.*, cavernous sinus. [From Duke-Elder (75).]

a glomerular tuft (21) and is covered by a double layer of epithelium, the outer layer of cells being pigmented. The ciliary processes obviously represent a region of expanded surface area—Baurmann calculated that, in man, the area was some 6 $cm^2$—and for this reason at least may be looked on as the source of the aqueous humor, although, as with the choroid plexuses, the evidence favoring this view is not unequivocal.

Drainage of the aqueous humor takes place by way of the canal of Schlemm into the venous system (fig. 8); the canal of Schlemm is a channel lying in the sclera at the corneoscleral junction. The wall of the canal consists of a delicate layer of endothelium; between the anterior chamber and this delicate membrane is the corneoscleral meshwork made up of a series of collagenous lamellae and rods, and the aqueous humor must pass through the spaces in this meshwork—the spaces of Fontana—in order to reach the canal. From the canal the fluid is carried by collectors into the vessels of the intrascleral venous plexus which is the deepest of four plexuses described by Maggiore (149) in the anterior segment of the eye (fig. 8). From this plexus, blood, diluted with aqueous humor, is carried more superficially in the episcleral and conjunctival veins to empty finally in the anterior ciliary veins. That the intraocular fluid was, indeed, drained away in this fashion was made very probable by Lauber's (140) observation that the blood from the anterior ciliary veins was considerably diluted by comparison with blood from an ear vein; later Seidel (206) showed that colored solutions, introduced into the anterior chamber, appeared rapidly in the anterior ciliary veins even when the intraocular pressure was held below normal. Seidel's work demonstrated very clearly that drainage by way of the canal of Schlemm was possible, and his careful measurements of the pressure in the anterior ciliary veins showed that there was a sufficient gradient of pressure between the anterior chamber and the venous system to permit a continuous flow. Unfortunately, Lauber's and Seidel's work was either ignored or dismissed by subsequent workers, e.g. Duke-Elder (76), so that the view that the aqueous humor was a stagnant fluid was maintained for some time. However, the discovery by Ascher (4–6) that drainage was not confined to an emptying into the deep intrascleral vessels but could occur directly into the more superficial episcleral and conjunctival veins, along what he called aqueous veins, re-established Seidel's view. Ascher observed among the superficial vessels of the globe what appeared to be empty veins; a careful study indicated, however, that they contained aqueous humor and, on following them peripheral-wards, they could usually be seen to empty into blood-filled veins, in which case it frequently happened that the two currents did not mix immediately but remained separate to give a laminated aqueous vein (fig. 9). Subsequent study of these vessels by a great many workers[7] has fully confirmed

[7] The literature relating to the aqueous veins is very large and repetitive. Goldmann (105, 106, 109) provided the unequivocal proof that the veins contained aqueous humor by injecting fluorescein into the blood. While the blood-veins fluoresced strongly, the aqueous veins did not because fluorescein penetrates only very slowly into the aqueous humor. Thomassen (221) showed that in a human eye, the introduction of methylene blue into the anterior chamber caused the aqueous

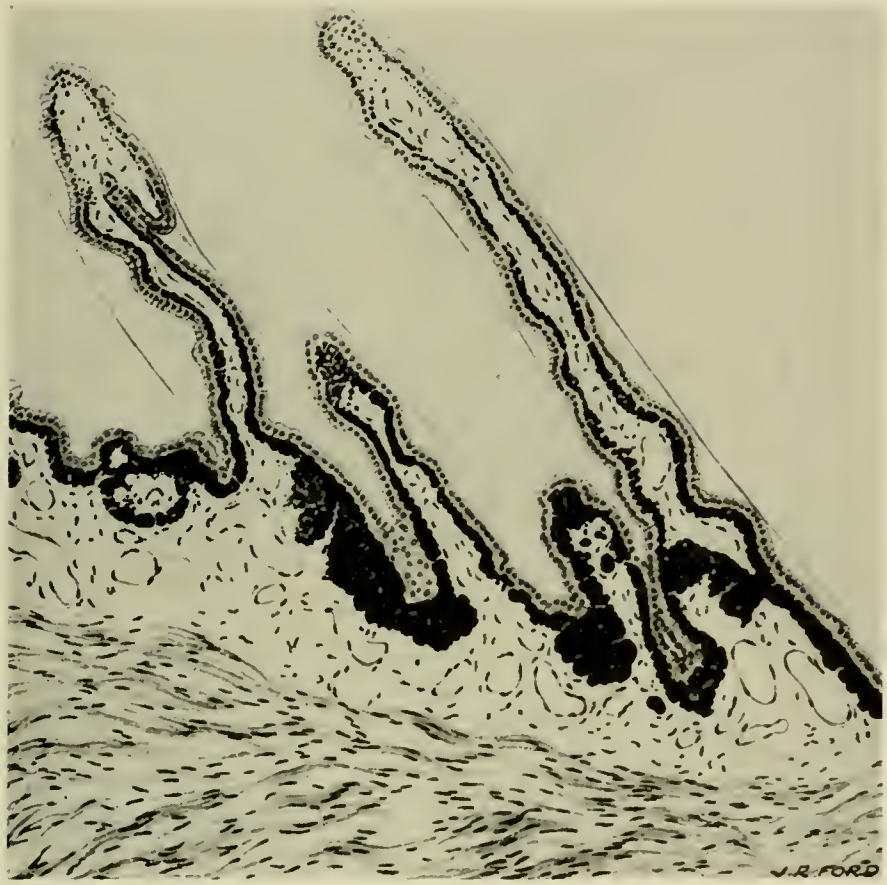



FIG. 7. Oblique section of the human ciliary body. [From Wolff (253).]

Ascher's belief that they represent visible channels for drainage of the aqueous humor, and the circumstance that their presence may be repeatedly detected in the same place in the same subject indicates that drainage is a continuous process, i.e. that the aqueous humor, like the cerebrospinal fluid, is constantly being renewed.

We may thus picture the circulation of the aqueous humor as a primary elaboration of the fluid in the posterior chamber by the epithelium of the ciliary body, associated with a flow over the lens and through the pupil into the anterior chamber where it percolates through the trabecular meshwork in the angle and across the endothelial lining of Schlemm's canal. From Schlemm's canal the fluid empties into the venous system; some of the aqueous humor may travel in aqueous veins to reach the superficial episcleral and conjunctival veins, while the remainder is carried by short collectors which empty at once into the veins of the intrascleral plexus. On this view, then, the main regions of interchange between blood and aqueous humor are in the ciliary processes and in the angle of the anterior chamber. The aqueous humor is in close contact with another vascular tissue, namely the iris, and it is reasonable to expect that exchange of material between blood and this fluid will take place here, the more so since in many species, including man, the anterior surface is not covered by any very well defined endothelial layer (229, 254) so that the aqueous humor may apparently percolate between the connective tissue cells of the anterior lamina to come into direct relationship with the capillary circulation. The actual role of the iris in the formation or absorption of the aqueous humor has been a matter of controversy; since colored substances, injected into the anterior chamber, appear in the anterior ciliary veins, and not the vortex

veins to become blue. Kleinert (135) has contributed useful information on the ramifications of the aqueous veins, while Ashton (8, 9) has actually dissected them out from neoprene casts of the canal of Schlemm. Useful reviews of this subject are those of Weinstein (245) and Ascher (7); their value in the experimental approach to glaucoma is indicated in Goldmann's comprehensive study (111).

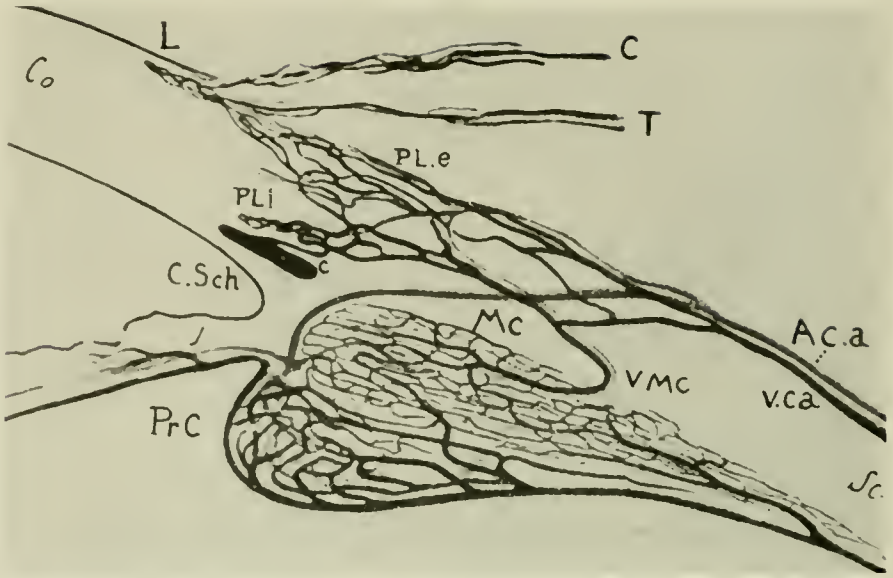



FIG. 8. Plexuses of the anterior segment of the eye. *C*, conjunctival plexus; *T*, Tenon's capsule plexus; *PL.e*, episcleral plexus; *PLi*, intrascleral plexus; *Mc*, ciliary muscle; *VMc*, vein of ciliary muscle; *Ac.a*, anterior ciliary artery; *V.ca*, anterior ciliary vein; *PrC*, ciliary process; *Co*, collector; *L*, limbus. [From Maggiore (149).

veins, it is unlikely that the iris is a site for any significant absorption of fluid;[8] as an auxiliary site for the formation of the fluid, the iris cannot be entirely ruled out, while, as we shall see, as a region in which rapid exchanges of dissolved material between blood and aqueous humor take place it may occupy a prominent position.

## CHEMICAL COMPOSITION OF INTRACRANIAL AND INTRAOCULAR FLUIDS

Both the aqueous humor and cerebrospinal fluid differ from plasma in one obvious respect, namely in their very low concentrations of protein; thus the approximate protein concentrations in man and the rabbit[9] are as follows:

| | Cerebrospinal Fluid | Aqueous Humor |
|---|---|---|
| Man | 25 mg per 100 ml | 13 mg per 100 ml |
| Rabbit | 25 mg per 100 ml | 31 mg per 100 ml |

By contrast, there are some 6500 to 7500 mg of protein per 100 ml in the plasma. It immediately becomes clear, however, that the fluids are not simple plasma filtrates when we compare the ratios of the concentration in fluid and the concentration in plasma with those found experimentally for plasma dialysates (table 1). Thus, to choose some of the more obvious discrepancies, it will be seen that the cerebrospinal fluid has higher concentrations of sodium and chloride than are found in a plasma dialysate, while the con-

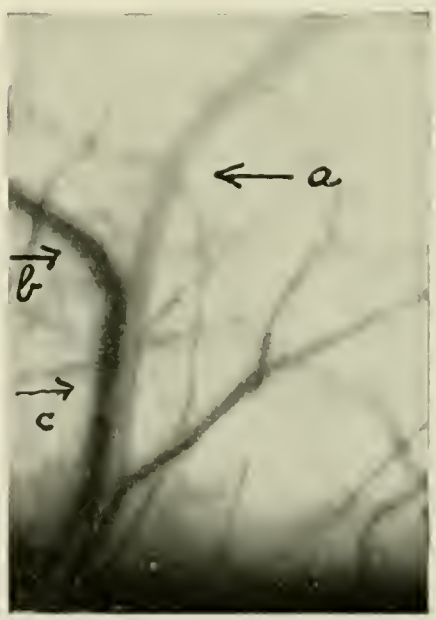



FIG. 9. Photograph of an aqueous vein. *a*, pure aqueous vein, *b*, blood vein; *c*, laminated vein. [From Weinstein (245).]

[8] The vortex veins drain all the blood from the iris, while Schlemm's canal empties, ultimately, into the anterior ciliary veins.

[9] The cerebrospinal fluid from the rabbit was obviously a mixed sample of ventricular and subarachnoid fluids since about 1 ml was drawn from the cisterna magna. The figure quoted for the protein concentration in human cerebrospinal fluid (186) applies to lumbar fluid; ventricular fluid has a lower concentration (43).

TABLE 1. *Distribution in the Rabbit of Various Ions and Nonelectrolytes*

[After Davson (59)]

| Substance | $R_{Aq}$* | $R_{Csf}$† | $R_{Dial}$‡ |
|---|---|---|---|
| $Na^+$ | 0.96±0.01 | 1.03±0.005 | 0.945±0.003 |
| $K^+$ | 0.955±0.02 | 0.52±0.04 | 0.96±0.005 |
| $Mg^{++}$ | 0.78±0.04 | 0.80±0.05 | 0.80±0.02 |
| $Ca^{++}$ | 0.58±0.005 | 0.33±0.01 | 0.65±0.02 |
| $HCO_3^-$ | 1.26±0.03 | 0.97±0.04 | (1.04) |
| $H_2CO_3^-$ | 1.29 | 1.61 | (1.00) |
| $Cl^-$ | 1.015±0.01 | 1.21±0.007 | 1.04±0.006 |
| $Br^-$ | 0.98±0.015 | 0.715±0.02 | 0.96±0.01 |
| $I^-$ | 0.32–0.51 | 0.004–0.04 | 0.85–0.01 |
| $CNS^-$ | 0.46–1.24 | 0.06–0.21 | 0.59 |
| Phosphate | 0.58±0.05 | 0.34±0.05 | |
| Glucose | 0.86±0.25 | 0.64±0.02 | 0.97±0.01 |
| Urea | 0.87±0.02 | 0.81±0.02 | (1.00) |
| Ascorbic acid | 18.5 | 1.55 | (1.00) |
| pH | 7.48 | 7.27 | 7.46 (plasma) |

* Between aqueous humor and plasma; † between cerebrospinal fluid and plasma; ‡ between plasma dialyzate and plasma; where R represents the ratio between the concentration in fluid water and the concentration in plasma water.

Figures in parentheses are assumed values, no measurements being recorded in the literature.

TABLE 2. *Distribution of Chloride and Bicarbonate in Various Mammalian Species*

[From Davson and Luck (58, 63)]

| Species | Chloride | | Bicarbonate | |
|---|---|---|---|---|
| | $R_{Aq}$* | $R_{Csf}$† | $R_{Aq}$* | $R_{Csf}$† |
| Horse | 1.14 | 1.19 | 0.82 | 0.92 |
| Ox | 1.15 | | | |
| Sheep | 1.16 | | | |
| Goat | 1.09 | 1.09 | 0.67 | 0.81 |
| Monkey | 1.09 | 1.11 | 0.77 | 0.78 |
| Dog | 1.07 | 1.11 | 1.13 | 0.92 |
| Cat | 1.055 | 1.15 | 1.27 | 0.93 |
| Rabbit | 1.01 | 1.21 | 1.28 | 0.94 |
| Guinea pig | 0.935 | 1.18 | 1.35 | 0.91 |
| Rat | 1.025 | | 1.15 | 0.96 |

* Between aqueous humor and plasma; † between cerebrospinal fluid and plasma.

centrations of bicarbonate, potassium, phosphate, calcium, glucose and urea are less than in such a dialysate. In the rabbit, to which the figures in table 1 apply, the concentration of magnesium in the cerebrospinal fluid is the same as in the dialysate, but in man the concentration is considerably higher so that the ratio $R_{Csf}$ is of the order of 1.13 (156) to 1.30 (137). Owing to the binding of magnesium to the plasma proteins as an unionized complex, the value of $R_{Dial}$, the distribution ratio for a plasma dialysate, is 0.80; in man, therefore, the cerebrospinal fluid has a very large excess of magnesium over that in a dialysate of plasma. The aqueous humor of the rabbit is characterized by obvious excesses of bicarbonate and ascorbic acid, by comparison with a plasma dialysate, while chloride, calcium, glucose and urea are deficient. These features of the chemical compositions of the two fluids are sufficient to emphasize that both may be regarded as secretions in the sense that osmotic work must be performed during their elaboration. The results described in table 1 apply to the rabbit, the only species in which an exhaustive study of the two fluids, drawn from the same animals, has been carried out. With the exception of the distribution of magnesium, discussed above, the chemical composition of the cerebrospinal fluid does not show wide variations with different species; in the eye, however, some striking species variations in the distributions of certain substances, notably chloride and bicarbonate, have been found, as shown in table 2.

It will be seen that in the guinea pig and rabbit the distributions of chloride are such that the aqueous humor has a deficiency of this ion by comparison with a dialysate of plasma ($R_{Dial}$ averages about 1.04), while the horse, dog, goat, etc. have excesses of chloride; in general, those species exhibiting an excess of chloride show a deficiency of bicarbonate, although the cat and dog have small excesses of both ions. A clue to these variations in distribution of chloride and bicarbonate is given by plotting the value of the distribution ratio for chloride against the weight of the eye, as in figure 10. It will be seen that there is a broad correlation between eye size and the magnitude of the ratio—i.e. the magnitude of the excess of chloride in the aqueous humor —the largest excess being found in horse and ox eyes. The cerebrospinal fluids of all species, from the rat to the horse, have chloride and bicarbonate distributions corresponding roughly with those characteristic of the aqueous humor of the large-eyed animals. If we regard the cerebrospinal fluid as the typical cavity-filling fluid, then we may say that the aqueous humors of the small-eyed guinea pig and rabbit have undergone some modifications to meet the special requirements of small eyes. As to what all these requirements are is not immediately evident, but one becomes

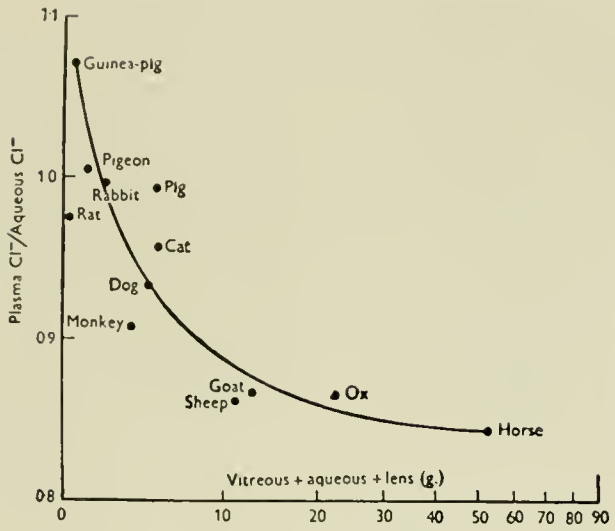



FIG. 10. Variation in the chloride distribution ratio: conc. in plasma/conc. in aqueous humor (i.e. $1/R_{Aq}$) with weight of the intraocular contents. [From Davson *et al.* (66).]


FIG. 11. Outlines of meridional sections of eyes of various mammalian species, drawn to scale; note the differing proportions of the globe contents occupied by the lens. [From Davson & Luck (62).]

prominent on examining anteroposterior sections of the eyes of different mammalian species, as in figure 11. It will be seen that a small eye is associated with a lens that is large in proportion to the total ocular contents; since the lens continually produces lactic acid, the adequate buffering of the ocular contents of the small eye becomes a problem which is met by the secretion of increasing concentrations of bicarbonate in the aqueous humor. A second factor may well be the total osmotic pressure of the aqueous humor in relation to that of the plasma; this point will be discussed later (p. 1780) and here it need only be indicated that the variations in the excesses of chloride in the aqueous humors of the different species may represent, to some extent, variations in the difference of osmotic pressure between aqueous humor and plasma, an important factor when the intraocular pressure is considered.

## BLOOD-AQUEOUS, BLOOD-CEREBROSPINAL FLUID AND BLOOD-BRAIN BARRIERS

Although this brief summary of the chemical composition of the aqueous humor and cerebrospinal fluid indicates that they are formed by a process of secretion—presumably by the epithelial linings of the ciliary body and the choroid plexuses—this does not mean that their constitution at any given moment is independent of variations in the concentrations of the constituents of the blood plasma. To understand the true relationships between the blood and the two fluids under consideration, a thorough knowledge of the possibilities of exchange between them and the blood plasma is necessary, in other words, a knowledge of the nature of the blood-fluid barriers. The early work on this subject was largely confined to a study of the ability, or otherwise, of dye-stuffs to pass from the blood into the fluid; at best, the results of such studies were equivocal, and generally they were misleading, so that nothing will be lost if in the present discussion we confine ourselves to the consideration of more recent studies in which substances of well-defined chemical constitution have been employed. The technique for the quantitative study of the blood-fluid barriers consists generally of maintaining a definite concentration in the plasma of the substance to be examined and determining, after an appropriate interval, the concentration in the fluid. By a suitable mathematical analysis a parameter, $k$, may usually be computed, indicating the rate at which the fluid comes into equilibrium with the plasma so far as this particuar substance is concerned. Thus, a high value of $k$ indicates that the various membranes, or barriers, separating the plasma from the fluid are easily permeated by the substance so that the attainment of equilibrium is rapid; a low value of $k$ indicates the reverse.

### *Blood-Aqueous Fluid Barrier*

Some of the results of quantitative studies of this barrier are shown in table 3. It will be clear that the

TABLE 3. *Values of $k_{In}$ for Rabbit Aqueous Humor**

[After Davson (58)]

| Substance | $k_{In}$ (min.$^{-1}$) |
|---|---|
| Sucrose | 0.00072 |
| Creatinine | 0.0022 |
| Thiourea | 0.0082 |
| Methyl thiourea | 0.0115 |
| Ethyl thiourea | 0.0144 |
| Propyl thiourea | 0.0220 |
| Ethyl alcohol | 0.0500 |
| Sodium | 0.0080 |
| Bromide | 0.0104 |
| Thiocyanate | 0.0130 |
| Potassium | 0.0104 |

* $k_{In}$ being the transfer constant in the equation $\frac{dC_{Aq}}{dt} = k_{In}C_{Pl} - k_{Out}C_{Aq}$, where $C_{Aq}$ and $C_{Pl}$ are the concentrations in the aqueous humor and plasma, respectively.

ability to penetrate the blood-aqueous barrier depends critically on the nature of the molecule or ion that has to pass across the barrier which is in marked contrast to the state of affairs when the passage across the capillaries into the interstitial fluid of muscle is considered. Under these conditions the rates of penetration are so similar that it is difficult experimentally to ascertain that there are indeed any differences. In general, it is considered that the passage from blood to interstitial fluid of muscle is determined by the ability of the substance to pass out of the blood capillaries and this, in turn, is thought to consist of a passage through the relatively large spaces between the endothelial cells of the capillaries. These spaces are large by comparison with noncolloidal molecules so that the capillary membrane as a whole offers very little restraint to their diffusion into the outside extracellular fluid. If sodium, urea and glucose were studied, for example, their respective rates of escape from the capillary would certainly not differ by more than a factor of two. The very large differences in rates of penetration of the blood-aqueous barrier, shown in table 3, are thus more reminiscent of the phenomena of cellular permeability than of capillary permeability. When substances penetrate from the outside of a cell to the inside, or in the reverse direction, they have to pass through the fatty envelope, or plasma membrane, of the cell. The ability to do this varies enormously with different molecular types and depends critically upon the chemical constitution of the molecule or ion under consideration. In particular, the factor of lipoid solubility is of importance, highly lipoid-soluble substances penetrating rapidly through cell membranes. It will be seen from table 3 that highly lipoid-soluble substances, like ethyl alcohol and the substituted thioureas, penetrate the blood-aqueous barrier relatively rapidly, while the lipoid-insoluble substances, like sucrose, penetrate much more slowly. These results indicate, in a general way, that passage from blood into aqueous humor is to a large extent determined by a passage across cellular membranes; thus on the basis of this finding one is inclined to ascribe the barrier existing between blood and aqueous humor to the epithelial layer of cells lining the ciliary body. If the capillaries in the ciliary body were similar to those in muscle, they would not exert a serious restraint on the passage out of the blood into the extracellular fluid of this body. The epithelium, consisting of two layers of closely packed cells, would, on the other hand, be expected to offer a restraint, since the substance would most probably have to pass through the cells, i.e. across the plasma membranes. The fact that the iris is not covered by a closely packed epithelial layer on its anterior surface might lead one to expect that diffusion from the blood into the aqueous humor would not be the highly specific phenomenon actually observed. One would expect the substance to diffuse rapidly out of the capillaries of the iris and thence, without encountering a further barrier, into the fluid in the anterior chamber. The fact that penetration of the barrier is so highly specific forces one to one of several conclusions: *a*) the capillaries of the iris—and possibly also of the ciliary body—are fundamentally different from those in muscle; *b*) the capillaries are not different, but the degree of vascularization of the iris is so poor that the amounts of material escaping by way of the iris are small compared with the amounts passing out of the ciliary processes where the vascularization is relatively enormous; or *c*) the capillaries of the iris are not different, but the feltwork of connective tissue cells on the anterior surface of the iris itself constitutes a serious barrier to diffusion. One may not be dogmatic on this point, but it would seem that the two last factors provide the explanation for the highly specific nature of the permeability of the blood-aqueous barrier.

Beside permitting us to say that permeability of the blood-aqueous barrier is a highly specific phenomenon, modern quantitative studies have enabled us to build up the following picture of the modes of penetration of different substances from blood into the aqueous humor.

*a*) The substance diffuses out of the capillaries of

the ciliary body to enter the secretory cells of the epithelium; these cells are continually ejecting a fluid—the primary aqueous humor—into the posterior chamber. The greater the ease with which a substance may pass into these cells, the greater will be the concentration in the secretion and thus the greater the rate at which it passes into the aqueous humor. Ultimately, however, the rate of flow of fluid will provide an upper limit to the rate at which the substance may enter the aqueous humor, unless there is a subsidiary mode of penetration.

*b*) Such a route is provided by diffusion of the substance out of the capillaries in the iris and thence, through or between the mass of connective tissue cells, into the fluid in the anterior chamber. Here, again, lipoid solubility probably plays a part since the ability to pass through the iris may depend critically upon the ability of the molecule to pass through—rather than around—the connective tissue cells.

*c*) Certain substances, like the plasma proteins and rather large water-soluble molecules, e.g. those of sucrose, inulin and *p*-aminohippurate, cannot be expected to pass into cells, and their ability to cross the blood-aqueous barrier must depend on their ability to pass through intercellular spaces, i.e. between the cells of the ciliary epithelium. If the number and size of these leaks are limited, the rate of penetration of the barrier by substances confined to this mechanism may be very small indeed.

Accordingly, the greater the extent to which a substance may use all these routes into the aqueous humor, the greater will be the rate at which the plasma comes into equilibrium with the aqueous humor when the concentration of this substance in the plasma is altered (or vice versa). Thus alcohol penetrates cell membranes very rapidly and when a high concentration is established in the plasma the concentration in the aqueous humor rises to that in the blood very rapidly (168); in this case all three routes are doubtless available. Sucrose penetrates the barrier slowly; it presumably uses only the third route. Urea penetrates more rapidly than sucrose but much less rapidly than alcohol; there is reason to believe that its main route of entry is in the primary secretion, very little entering by the other two routes.

### *Blood-Cerebrospinal Fluid Barrier*

It is only recently that quantitative studies on the blood-cerebrospinal fluid barrier have been made, largely as a result of the availability of isotopes (31–33, 77, 116, 218–220, 224). A simultaneous study of the penetration of a variety of substances in both the aqueous humor and cerebrospinal fluid of the rabbit (57, 58) gave the values of $k$ shown in table 4. It will be seen that the same general rule applies to both systems, namely that penetration is highly specific and that lipoid solubility is a dominant factor. By applying the same sort of analysis as that employed with the results on the aqueous humor, the process of penetration into the cerebrospinal fluid may be described in terms of similar mechanisms, namely penetration into the primary secretion in the ventricles, penetration directly from blood independently of this secretion (analogous to the direct diffusion across the iris) and finally, leakage through large pores permitting the passage of large water-soluble molecules including the plasma proteins. The question of greatest interest is what is meant by the direct diffusion into the cerebrospinal fluid. This must occur mainly in the subarachnoid space, and one may ask whether the diffusion occurs directly from the vessels of the pia or less directly from the capillaries of the nervous tissue and subsequent diffusion from the extracellular fluid of this tissue into the cerebrospinal fluid. To resolve this we must know what happens to the substances passing from the blood to the nervous tissue. Does the concentration in this tissue keep pace with that in the cerebrospinal fluid, or does it keep ahead, or lag behind? If the concentration is ahead, clearly there will be the possibility of a diffusion from nervous tissue to the cerebrospinal fluid; whereas if the concentration in the tissue lags behind, the latter will gain material from the cerebrospinal fluid. We are therefore concerned with the blood-brain-barrier—the ease with which substances pass out of the blood into the central

TABLE 4. *Values of $k_{out}$ Deduced from Curves of Penetration into the Aqueous Humor and Cerebrospinal Fluid of the Rabbit*

[After Dawson (58)]

| Substance | $k_{out}$ | |
|---|---|---|
| | Aqueous humor | Cerebrospinal fluid |
| Thiourea | 0.00965 | 0.0057 |
| Methyl thiourea | 0.0125 | 0.0135 |
| Ethyl thiourea | 0.015 | 0.021 |
| Propyl thiourea | 0.022 | 0.035 |
| Ethyl alcohol | 0.050 | 0.225 |
| $Na^{24}$ | 0.0090 | 0.0041 |
| $Br^{82}$ | 0.0120 | |

nervous tissue. Although the blood-brain barrier has been the theme of many hundreds of papers, it has been only recently that anything of a quantitative nature has been published on it. Wallace & Brodie (230) provided the answer to our problem, so far as the bromide, iodide and thiocyanate ions are concerned, by showing that when these ions were injected into the blood, they came into equilibrium with the extracellular space of the nervous tissue at approximately the same rate as with the cerebrospinal fluid. A more comprehensive study (58) extended to substances of varying lipoid solubility showed that with lipoid-insoluble substances, for example the isotope $Na^{24}$, the picture described by Wallace & Brodie was correct, $Na^{24}$ coming into equilibrium with the extracellular space of the nervous tissue at the same rate as with the cerebrospinal fluid. With lipoid-soluble substances, on the other hand, the nervous tissue came into much more rapid equilibrium so that at any given moment during the process of equilibration with the plasma, the cerebrospinal fluid lagged behind badly. Hence the concentration of the lipoid-soluble substance in the tissue adjoining the cerebrospinal fluid was always such as to favor diffusion from the tissue into the fluid, either in the ventricle or in the subarachnoid space. Water exchanges very rapidly between blood and cerebrospinal fluid (219) and, as with the lipoid-soluble substances, its rate of equilibration between plasma and nervous tissue is very much more rapid than between plasma and cerebrospinal fluid (31). In general, then, we may say that when a substance is injected into the blood, it passes into the nervous tissue directly across the blood-brain barrier; it passes into the cerebrospinal fluid by way of the choroid plexuses and possibly from the vessels of the pia. During the approach to equilibrium, i.e. the equalization of concentrations between plasma and fluids, the concentrations in the extracellular fluid of the nervous tissue and in the cerebrospinal fluid will not always be the same. If the substance is a rapid penetrator, like ethyl alcohol, the concentration in the nervous tissue will be higher than in the cerebrospinal fluid, and the latter will be assisted in its approach to equilibrium by diffusion from the nervous tissue. With ions, and probably with a number of lipoid-insoluble nonelectrolytes, it would seem that the concentrations remain sufficiently close so that significant movement of material from one system to the other does not occur. With certain other substances, it may well be that the concentration in the nervous tissue lags behind that in the cerebrospinal fluid so that the latter may be said to be the source of some of the material reaching the nervous tissue from the blood.[10] This would appear to be true of inorganic phosphate; if this ion, 'tagged' with $P^{32}$, is injected into the blood, its penetration into the cerebrospinal fluid and the nervous tissue is slow (13, 39, 116, 185). When the inorganic phosphate is introduced directly into the subarachnoid space, it is rapidly taken up by the nervous tissue (14, 193) where it is incorporated into organic complexes. Consequently, when inorganic phosphate is injected into the blood, because the phosphate passing across the blood-brain barrier is rapidly incorporated into complexes by the nervous tissue, the concentration in the extracellular fluid of this tissue may be expected to be always lower than in the cerebrospinal fluid so that diffusion of phosphate from the cerebrospinal to the extracellular fluid will occur. In other words, in this case the cerebrospinal fluid acts as a transporting medium for inorganic phosphate from blood to nervous tissue, augmenting the amounts that pass directly across the blood-brain barrier.

It must be borne clearly in mind that these conclusions, derived from kinetic studies of the blood-cerebrospinal fluid and the blood-brain barriers, tell us little as to the possibilities of the flow of fluid from one compartment to the other. Thus the literature contains many references to a subsidiary source of the cerebrospinal fluid derived from the nervous tissue, but the circumstance that a substance diffuses from the nervous tissue to the cerebrospinal fluid during the approach to equilibrium with the plasma does not mean that there is necessarily, or even probably, a flow of fluid in this direction. All that the experiments show is that gradients of concentration may exist, and from this circumstance it follows that diffusion will occur down these gradients.

*Blood-Brain Barrier*

As revealed by the simultaneous measurements of penetration into the cerebrospinal fluid and nervous tissue described above, this barrier has qualitatively the same characteristics as the blood-cerebrospinal fluid and blood-aqueous humor barriers, the factor of lipoid solubility being dominant in determining ease of escape from blood to nervous tissue. Where lipoid-insoluble molecules and ions are concerned, quite large differences in rates of penetration into the nervous tissue are observed, as with the other barriers. In certain regions of the nervous system, however, the

[10] Stern & Gautier (212–214) considered that the cerebrospinal fluid was the sole source of material passing from blood to the central nervous tissue.

barrier between brain and nervous tissue is either reduced or nonexistent; these are the posterior lobe of the hypophysis (203), the area postrema in the roof of the fourth ventricle (251), the pineal body (148), the paraphysis (179), the wall of the optic recess (29) and the eminentia saccularis of the hypophyseal stem (250). When trypan blue is injected into the blood, it does not normally stain the nervous tissue (103); but in these special regions, which are essentially nonnervous regions of the central nervous system, the dye leaves the vascular system and is taken up in visible amounts. Subsequent work in which $P^{32}$-labeled inorganic phosphate (11, 12, 185) and bromide (117) were employed has confirmed that these regions are regions of increased permeability of the blood-brain barrier. Whether the low blood-brain barrier in these regions has any special physiological significance so far as function of the brain as a whole is concerned, or whether it is an accident following from the circumstance that the tissue in these regions is essentially nonneural, is a matter that cannot yet be decided.

### *Penetration into Different Regions of Cerebrospinal System*

We have so far treated the cerebrospinal fluid as a whole. When it is appreciated that this fluid not only occurs in the ventricles but is spread over the whole surface of the central nervous system, it will not be surprising to find that when a substance is injected into the blood, it will find its way into some regions more rapidly than into others. Thus, if our present viewpoint is correct, the most important site of penetration is in the ventricles. It is here that the fluid is primarily secreted so that if a substance penetrated from blood to fluid predominantly in this primary secretion, and only secondarily by direct diffusion into the subarachnoid fluid, we should expect to find a very marked degree of inhomogeneity in the fluid during the approach to equilibrium. Studies on man have, indeed, shown that all parts of the cerebrospinal system do not come into equilibrium with the blood at the same rate. Intravenous $Na^{24}$, for example, comes into equilibrium more rapidly with the ventricles than the cisternal or lumbar fluids (219, 220, 224). Water, alcohol and ethyl thiourea are very rapid penetrators of the barriers. This means that the direct penetration into the subarachnoid fluid must be very significant, so that we might expect a more uniform approach to equilibrium. Actually the subarachnoid fluid comes into equilibrium more rapidly than the ventricular, so far as water and alcohol are concerned (31, 219); with ethyl thiourea, the equilibration is almost uniform (57, 58).[11]

### *Breakdown of Barriers*

The aqueous humor and the cerebrospinal fluid normally contain small concentrations of the albumin and globulin fractions of the plasma proteins.[12] Analysis of the fluids in the anterior and posterior chambers (205) has shown that the posterior chamber fluid contains proteins in about the same concentration as in the anterior chamber so that we may assume that during the elaboration of the primary fluid appreciable amounts pass from the ciliary processes—presumably between the epithelial cells—to mix with the fluid elaborated by the cells. A similar state of affairs probably exists in the ventricles. That the fluids are constantly being drained away must mean that the wall of Schlemm's canal and the mesothelial lining of the arachnoid villus are permeable to these large molecules; if they were not, they would be retained and the concentration of proteins would build up to values comparable with those in the plasma. The globulin molecule is considerably larger than that of the albumin, however, and it may be that the generally higher values for the albumin globulin ratios found for the fluids reflect the tendency for the globulin molecules to be filtered back to a small extent in the drainage channels.[13]

When aqueous humor is withdrawn from the anterior chamber, the latter rapidly refills so that within

[11] Eichler & Linder (77) examined the penetration of $Na^{24}$ from the blood into different regions of the spinal subarachnoid; according to them, the lumbar region was the most favored and they argued that there was a lumbar source of secretion of the fluid. Their results with injections directly into the spinal arachnoid certainly suggested a cranially directed flow. Becker (24, 25) disputes the conclusions of Eichler & Linder. [See also Eichler *et al.* (78).]

[12] The various fractions of the proteins in the fluids have been analyzed by electrophoretic methods, they would appear to correspond with those in the plasma although the albumin/globulin ratio is usually higher in the fluid. [See von Sallmann & Moore (227), Witmer (252), Niedermeyer (165), Munich (164) and Esser *et al.* (80) for the aqueous humor; and Kabat *et al.* (129), Scheid & Scheid (197, 198), Esser & Heinzler (79) and Rossi & Schneider (192), among many others, for the cerebrospinal fluid.

[13] It may also be due to the more rapid penetration of the albumin molecules into the fluid. The problem as to the limiting size of the particles that may leave the anterior chamber has been examined experimentally by Huggert and his co-workers (124, 125), and by François *et al.* (90).

half an hour the pressure may be back to normal.[14] The newly formed 'plasmoid aqueous humor' contains a high concentration of protein and may best be described as aqueous humor mixed with plasma exudate. Clearly, the blood-aqueous barrier, which normally permits only traces of protein to escape into the fluid, has broken down. The exudation probably occurs mainly from the capillaries of the ciliary body (205) which becomes edematous. Histological study of the epithelium shows the appearance of characteristic vesicles (115, 176, 188) which are presumably full of plasma exudate; they apparently burst, ejecting their contents into the posterior chamber. The effect of emptying the anterior chamber is due to the sudden fall in intraocular pressure, permitting a sudden dilatation of the capillaries of the ciliary body, since the effect is most pronounced in eyes that contain relatively large volumes of aqueous humor, for example those of the cat (1). A similar breakdown may be caused by a variety of drugs and mechanical insults, and the feature common to all these interventions is, apparently, a dilatation of the vessels of the ciliary body and iris (247). As a result of the breakdown of the barrier, the chemical composition of the aqueous humor becomes closer to that of the plasma, for example the chloride (69), urea (160), and glucose (70, 71) concentrations alter in this direction. Essentially the breakdown of the barrier represents the development of more than the normal number of leaks in the barrier, leaks that normally permit a limited degree of admixture of plasma proteins with the secreted aqueous humor. It is not surprising, therefore, that the most obvious manifestation of the breakdown is the increased quantity of protein in the fluid. We may expect, furthermore, to find the rates of penetration of the barrier affected to different extents by the breakdown, according as the substance can make use of the various routes from plasma to aqueous humor discussed earlier. Thus, the effects of a breakdown will be large with sucrose and *p*-aminohippurate but small with a lipoid-soluble substance such as sulphanilamide (65).[15]

[14] Actually the pressure may rise above normal (205); this is presumably due to the blockage of the escape route by the fibrinogen that passes into the anterior chamber in the reformed fluid (259).

[15] The breakdown of the carrier is most commonly studied by measuring the rate of penetration of fluorescein into the eye; this normally penetrates very slowly, mainly because it is largely adsorbed to the plasma proteins (70, 71, 110). A breakdown of the barrier therefore has a large effect on the rate of penetration of this dyestuff. [For a useful review of the clinical applications of this test see Weinstein & Forgács (246).]

Withdrawal of cerebrospinal fluid has no such obvious effect on the blood-cerebrospinal fluid barrier, presumably because the fall in pressure is not so pronounced; inflammatory conditions and a number of other insults do lead to an increased concentration of protein in the fluid. The proteins are obviously derived from the plasma (129), and it is considered that the breakdown in the barrier is a reflection of an increased permeability of the pial blood vessels, although the involvement of the central nervous tissue and the choroid plexuses should not be excluded. As with the plasmoid aqueous humor, the composition of cerebrospinal fluid, under these conditions, appears to approach more closely that of plasma, the concentration of magnesium falling (49) and that of phosphate (48, 98) and potassium (147, 181) rising. Exogenous bromide is normally distributed between blood and cerebrospinal fluid to give a much lower concentration in the latter fluid (126, 230, 231); in meningitis, the concentration rises. The commonly accepted explanation for the changes in concentrations in meningitis is along the lines already indicated in interpreting similar changes in the plasmoid aqueous humor, namely that the breakdown of the barrier permits the readier diffusion from blood to cerebrospinal fluid, so canceling, to some extent, the effects of the primary secretion in the ventricles. The behavior of chloride is interesting in this respect. As we have seen, the concentration in the normal cerebrospinal fluid is much higher than in a dialysate of plasma; a breakdown in the barrier might be expected to cause the concentration to fall. In fact, the concentration of chloride in the cerebrospinal fluid is abnormally low in meningitis (159, 166) but, as Linder & Carmichael (142) first showed, and Wright *et al.* (258) and Fremont-Smith *et al.* (93) later confirmed, the fall in chloride concentration in the cerebrospinal fluid is associated with a concomitant fall of that in the plasma so that the value of $R_{Csf}$ remains substantially unchanged. If the barrier is abnormal in meningitis—and the evidence strongly suggests this—then we must conclude that the high concentration of chloride in the cerebrospinal fluid is not merely a sign of secretory activity on the part of the choroid plexuses, but that it is also maintained by the secretory activity of the cells of the nervous or glial tissue. A breakdown of the barrier, permitting a freer exchange between the blood and the cerebrospinal fluid, would tend to cause a fall in the concentration of chloride in the cerebrospinal fluid, but if the extracellular fluid of the nervous parenchyma itself had a high concentration of chloride —maintained by the secretory activity of its cells—

then losses of chloride from the cerebrospinal fluid to the blood in the meninges would be rapidly compensated by diffusion from the nervous tissue into the cerebrospinal fluid.[16]

### *Rates of Flow of Cerebrospinal Fluid and Aqueous Humor*

The pathological conditions of hydrocephalus and glaucoma indicate unequivocally that the fluids are formed continuously, a serious interference with the drainage routes leading inevitably to a rise in the fluid pressure. The question now arises as to the assessment of the rate of renewal, or turnover, of the fluids. This is remarkably difficult in the ocular system since withdrawal of fluid from the eye results, as we have seen, in a breakdown of the blood-aqueous humor barrier. The fluid reformed under these conditions is abnormal, having stronger affinities with an exudate of plasma than with true aqueous humor. Consequently, a mere measurement of the rate of reformation of fluid after withdrawal would provide a most unsound measure of the normal rate of flow. Probably the most accurate measurements are those of Bárány & Kinsey (19) in the rabbit and of Goldmann (110) in man. Space will not permit a detailed description of the theoretical basis of their computations. Essentially they measured the rate at which certain substances passed out of the aqueous humor; the substances chosen were such that a direct loss by diffusion into the iris and ciliary body was unlikely, the substances leaving almost exclusively by flow into the canal of Schlemm. Results in the rabbit and man gave turnover rates between 1.4 and 1.2 per cent per min., respectively. Kinsey & Bárány (133) showed that the rate at which the isotope, $Na^{24}$, entered the aqueous humor from the blood was apparently equal to the rate of turnover of the fluid as a whole, i.e. that one may assume that most of the sodium entering the eye from the blood comes in the primary secretion from the ciliary body, direct exchanges between the iris and the anterior chamber being small by comparison. If the same finding applies to other species, the rates of renewal of fluid in various mammals are as given in table 5. In the rat, the rate of renewal is remarkably high.[17]

In the cerebrospinal system the loss of fluid does not result in a serious breakdown of the barrier so that more direct measurements of rate of flow are probably feasible. Such studies (83, 86, 91, 116, 152, 184) indicate, in general, a rate of flow of the order of 0.2 to 0.5 per cent of the total volume per min., i.e. considerably less rapid than that of the aqueous humor. From measurements of the rate of clearance of substances injected into the cerebrospinal fluid, for example those of Dandy & Blackfan (56) with phenolsulphonephthalein, one may calculate a turnover rate for the dog of the same order, namely 0.3 per cent per min. (59).

### *Mechanism of Drainage*

In the ocular system, the factors determining the speed of drainage will clearly be the difference in pressure between the fluid in the anterior chamber and the blood in the anterior ciliary veins into which the collectors from the canal empty—the so-called outflow pressure—and the frictional resistance to flow across the wall of the canal and along the channels leading to the large veins. Increasing the intraocular pressure, for example by pressure on the globe, increases the rate of flow, as observed in aqueous veins (107, 108) or by less direct methods (112). Under normal conditions the intraocular pressure is about 20 mm Hg, while the pressure in the episcleral veins is of the order of 10 to 14 mm Hg (207) and in a laminated aqueous

[16] The extent to which the central nervous parenchyma may determine the concentration of a given ion or nonelectrolyte in the cerebrospinal fluid has not been seriously considered so far. There is some indirect evidence suggesting that this factor cannot be ignored. Thus the concentration of chloride in the ventricular fluid is not greatly, if at all, different from that in the lumbar fluid (43; 59, p. 210). If the extracellular fluid of the parenchyma were simply a filtrate of plasma, the concentration of chloride in it would be less than that in the cerebrospinal fluid, and diffusion from the latter would be expected as the fluid flowed through the subarachnoid space; in other words, the subarachnoid fluid should have a lower concentration than the ventricular. The fact that no difference has so far been demonstrated would indicate that the chloride concentrations in the two fluids cerebrospinal and extracellular—were determined independently, in the cerebrospinal fluid by the secretory activity of the choroid plexuses and in the extracellular fluid by the activity of the neurons or neuroglial cells.

[17] This high rate of turnover may be related to the relatively low concentration of bicarbonate in rat aqueous humor. In such a small eye the problem of neutralizing the lactic acid formed by the bulky lens must be acute, and it would seem to be achieved by a very rapid renewal of aqueous humor (62, 63). Other studies on rates of renewal of aqueous humor are those of Moses & Bruno (161), Grant (112), Becker *et al.* (23), Bárány (16–18) and Ross (189, 190). Recent studies on the kinetics of penetration of $Na^{24}$ into the aqueous humor suggest that values of the rate of flow derived from these measurements are low (97, 134).

TABLE 5. *Rates of Turnover for $Na^{24}$ in Different Species*

| Species | $k_{out}$ (min.$^{-1}$) | | References |
|---|---|---|---|
| | Aqueous Humor | Cerebrospinal Fluid | |
| Goat | 0.014 | | Davson & Luck (63) |
| Monkey | 0.010 | | Davson & Luck (63) |
| Dog* | 0.025 | 0.0073 | Wang (232) |
| Dog | 0.013 | | Davson & Luck (63) |
| Cat* | 0.014 | | Davson *et al.* (61) |
| Rabbit | 0.0090 | 0.0041 | Davson (58) |
| Guinea pig | 0.016 | | Scholz *et al.* (201) |
| Guinea pig | 0.014 | 0.017 | Davson & Luck (63) |
| Rat | 0.024 | 0.019 | Davson & Luck (63) |
| Man* (ventricle) | | 0.023 | Tubiana *et al.* (224) |
| Man* (ventricle) | | 0.0085 | Sweet *et al.* (219) |
| Child (open myelocele) | | 0.016 | Calculated from results of Cox *et al.* (52) |

* These results were obtained on anesthetized animals.

vein some 10 to 11 mm Hg (111, 146) so that the physical condition for a continuous flow of fluid is satisfied. Whether the main loss of pressure from the anterior chamber to ciliary veins takes place across the scleral meshwork and the endothelium of Schlemm's canal, as argued by Goldmann (111), or more distally is not certain. Measurement of the pressure in Schlemm's canal (170) and the effects of removal of the meshwork (113) would suggest that the resistance occurs mainly along the collectors and aqueous veins, and this seems reasonable when it is appreciated that the holes in the trabecular meshwork, and in Schlemm's canal, must be large enough to permit the passage of the large serum globulin molecules so that the frictional resistance to the flow of fluid may not be high. In the cerebrospinal system, drainage is apparently by way of the arachnoid villi projecting into the dural sinuses; the cerebrospinal fluid pressure is normally greater than the pressure in the dural sinuses (26, 239) so that a flow of fluid out of the cerebrospinal into the venous system is mechanically feasible. It has been argued, however, that besides the difference between cerebrospinal fluid and dural sinus pressures, a further factor influencing drainage is the colloid osmotic pressure of the plasma proteins (236). In order that such an osmotic pressure, drawing fluid from the cerebrospinal to the venous system, may be operative, however, the membranes separating the contents of the arachnoid villus from the blood in the dural sinus must be impermeable to proteins; the facts that the plasma proteins are normally drained away, and that the plasma proteins after injection into the subarachnoid space appear rapidly in the blood (51, 218) make it very unlikely that the membranes separating the two fluids in the arachnoid villus are impermeable to proteins; so this factor must be ruled out.[18]

## FATE OF MATERIAL INJECTED INTO SUBARACHNOID SPACE

### *Cerebrospinal Fluid-Brain Barrier*

The fluid within the subarachnoid space is enclosed within mesothelial membranes, the layers of cells lining the arachnoid and pia. To the extent that these cellular layers constitute an impediment to free diffusion, we may say that there is a barrier between the cerebrospinal fluid and its underlying nervous tissue. Moreover, beneath the pia there is a thick layer of neuroglial cells which may also, to some extent, retard diffusion; it is customary to describe the 'membrane' separating the subarachnoid fluid from the nervous tissue as the 'pia-glia'. When a substance is injected into the subarachnoid fluid, there are at least two theoretical pathways of escape into the blood stream. First, there is the passage through the arachnoid villi, i.e. along the main drainage route. Since there is every reason to believe that proteins may pass by this route, we may expect all noncolloidal matter to pass out at roughly the same rate by this channel. If the rate of renewal of the fluid is some 0.5 per cent per min., then the rate of loss of material by this route should be of this order.[19] Secondly, there is a direct diffusion across the pia-glia so that the substance reaches the capillary

[18] Weed (236) replaced the cerebrospinal fluid of a cat with solutions containing varying concentrations of protein and found that the rate of flow of fluid into the cisterna magna from a reservoir maintained at constant height varied inversely with the concentration of protein. This seemed to indicate that the normal rate of outflow was determined by the colloid osmotic pressure of the cerebrospinal fluid; unfortunately, Weed was ignoring the osmotic influx from the nervous tissue into the cerebrospinal fluid. Thus, replacing the fluid with a solution containing a high concentration of protein will cause a flow of extracellular fluid from the nervous tissue into the subarachnoid space; this will raise the fluid pressure and reduce the influx from the reservoir.

[19] From the rate of disappearance of inulin from the subarachnoid fluid of the rabbit one may compute a turnover rate of about 0.5 per cent per min. (58). Inulin has such a large molecule that it is unlikely to diffuse across the mesothelial linings of the subarachnoid space, so that it is probably lost to the blood exclusively by flow through the arachnoid villi.

system of the cerebral and spinal circulations; once it arrives here—in the pericapillary space—its fate will be determined by the ease with which it may pass the brain-blood barrier (the blood-brain barrier in reverse). If it is lipoid soluble, it will pass rapidly into the circulation and disappear from the nervous tissue. If it is a water-soluble substance of large molecular weight, like sucrose, *p*-aminohippurate or phenolsulphonephthalein, it will escape only very slowly into the blood stream by this route;[20] moreover, its rate of loss from the subarachnoid space into the nervous tissue will be low because it will have difficulty in surmounting the cerebrospinal fluid-brain barrier. Consequently, if a series of substances is studied, for example serum albumin, inulin, sucrose, *p*-aminohippurate, creatinine, thiourea, methyl thiourea, ethyl thiourea and ethyl alcohol, we may expect the rates of disappearance to increase in this order. The very large molecular-weight substances, such as albumin and inulin, will escape probably exclusively by the arachnoid villi; the smaller sucrose, *p*-aminohippurate and creatinine molecules will escape mainly by the arachnoid villi, but some will leave through the pia-glia to the nervous tissue where it is held up by the brain-blood barrier. With the more lipoid-soluble thiourea, ethyl thiourea and ethyl alcohol, the escape into the nervous tissue becomes the more important. In general, these predictions are confirmed by experiment (56, 57, 218). The behavior of $P^{32}$-labeled inorganic phosphate is of special interest since it is involved in the metabolism of the nervous tissue, being rapidly incorporated into organic phosphates (141). When the labeled phosphate is injected into the blood stream, the uptake of phosphate by the nervous tissue is slow, a fact indicating that the blood-brain barrier to inorganic phosphate is high; when injected into the subarachnoid space, the uptake by the nervous tissue is very rapid (14) so that we may conclude that the passage of this ion across the pia-glia is easy by comparison with passage across the blood-brain barrier.[21]

Particulate matter, such as carbon particles, thorotrast, pantopaque, etc., would appear to be largely confined to the subarachnoid space after an intralumbar or intracisternal injection (92, 215, 233). In chronic experiments there is certainly some escape into the epidural tissue and along the sheaths of the spinal nerves [see, for example, Brierley (40)], but there is little doubt that such escape routes are insignificant as far as the fate of nonparticulate matter is concerned. The interpretation of the results of the injection of particulate matter is obscured, moreover, by the inflammatory reaction in the meninges (3, 81, 180, 257) and an associated communicating hydrocephalus (183, 204, 234).[22]

## SPECIAL FEATURES OF CHEMICAL COMPOSITION OF INTRACRANIAL AND INTRAOCULAR FLUIDS

The main outlines of the chemical composition of the fluids have been sketched earlier; by virtue of their chemical make-up, which differs from that of a dialysate of plasma in many respects, the fluids have been described as secretions; that is, taking either fluid as a whole, we may say that special active-transport mechanisms must have been operative during the process of their elaboration. This does not mean, of course, that every type of molecule or ion entering the fluid from the blood is subjected to special secretory activity; in fact there is good reason to believe that with many substances, in particular the relatively lipoid-soluble materials studied experimentally, simple diffusion processes are adequate to account for their

[20] In the specialized regions like the area postrema, where the blood-brain barrier is low or absent, we should expect these large molecular weight and lipoid-insoluble molecules to escape. Actually this has been found, although the phenomenon seems to have puzzled those who discovered it. Thus Woollard (257) and Mandelstamm & Krylow (151) noticed that these areas did not stain when trypan blue was injected into the subarachnoid space, although the rest of the brain was strongly stained. The blood-brain barrier being absent in these regions, any trypan blue diffusing into them must be carried away rapidly into the blood stream. An essentially similar phenomenon has been noted more recently (11, 12) with radioactive phosphate.

[21] These experiments with phosphate are essentially repetitions, in a more modern fashion, of the original Goldmann (103, 104) experiments: trypan blue did not pass from blood to nervous tissue, but when injected into the subarachnoid space the tissue was rapidly stained. Tschirgi (223) has shown that the interpretation of Goldmann's experiments is by no means unequivocal, however, owing to the binding of trypan blue to the plasma proteins, so that it is unfair to compare the passage of trypan blue from blood (where it is bound to the proteins) to nervous tissue, and from the cerebrospinal fluid (where it is free) to the nervous tissue. Experiments with $P^{32}$-labelled inorganic phosphate (13) and with $Na^{24}$ (57, 58, 218, 224) indicate quite unequivocally, however, that passage across the brain-cerebrospinal fluid barrier is less restricted than across the blood-brain barrier; this becomes especially apparent when we consider how much more favorable for diffusion are conditions in the capillary bed than in the subarachnoid space. The area of the capillary bed of the nervous tissue is many times greater than that of the surface of the central nervous system.

[22] The fate of the constituents of the blood, plasma proteins and erythrocytes has been investigated by Courtice & Simmonds (51) and Simmonds (208, 209). Red cells are very definitely eliminated from the subarachnoid space without a preliminary hemolysis; in this respect they stand out in marked contrast to inanimate particulate matter of comparable size.

steady-state distributions between plasma, on the one hand, and the aqueous humor and cerebrospinal fluid on the other. The main problem of the physiologist concerned with these specialized tissue fluids is to find out to what extent the steady-state concentration of any given constituent is determined by secretory activity in which it itself is directly involved, to what extent it is determined by secretory activity in which other substances are involved, and to what extent various other factors—such as the consumption, or synthesis, of the substance in the eye or cerebrospinal system—contribute. Space will not permit a detailed analysis of each component of the normal fluids, and even if it did, our knowledge is not sufficiently detailed to permit a clear exposition of all the factors determining the concentration of even one component. A few examples, however, will be of value in illustrating the complexities of the problems and the general modes of approach to their solution.

*Urea*

The concentrations of urea in the aqueous humor and cerebrospinal fluid are about 70 to 80 per cent of that in the plasma. When the plasma concentration is raised, either experimentally or pathologically, urea passes into both fluids (47, 54, 61), but the process is slow—in other words, the barriers to the penetration of urea are fairly high. It is possible, therefore, that during the elaboration of the primary secretion, the passage of urea from the plasma into the secretory cells is so slow that the concentration in the fluid as finally secreted does not reach that in the plasma. The low concentrations of urea in the fluids may thus be an accidental consequence of the low permeability of the secretory cells to this substance rather than to any specific secretory activity directed toward keeping urea out of the fluids. A similar state prevails with the even more slowly penetrating *p*-aminohippurate (19), sucrose (65), and creatinine and iodide (58). With more rapidly penetrating substances, such as thiourea and its substituted derivatives, some sulphonamides, and alcohol, the secretory cells may apparently reach equilibrium with the plasma so that the steady-state distribution is unity.[23]

*Glucose*

Glucose is a relatively rapid penetrator into both the aqueous humor and cerebrospinal fluid (58, 61, 119) so that we might expect to find it equally distributed between plasma and the fluids; yet we have seen that values of $R_{Aq}$ and $R_{Csf}$ in the rabbit are 0.86 and 0.64, respectively. The explanation for this is clearly the utilization of glucose by the lens and retina of the eye and by the nervous and glial tissue adjacent to the cerebrospinal fluid. Thus, the concentration in the vitreous body is considerably less than in the aqueous humor, presumably because the retina and lens are utilizing this metabolite. Newly formed aqueous humor may well have a concentration equal to that in the plasma; but because the fluid flows over the vitreous body and lens, it rapidly loses glucose and a steady-state is reached, with the aqueous humor and vitreous body having concentrations less than in the plasma.[24]

*Phosphate*

The concentration of inorganic phosphate is low in both aqueous humor and cerebrospinal fluid. The rates of penetration from the plasma are apparently slow so that, at first thought, we might attribute the low concentrations to a slow penetration into the secretory cells, as with urea, sucrose, etc. However, the concentration in the vitreous body is considerably less than in the aqueous humor (44, 211, 222), and this suggests that the retina is continually removing inorganic phosphate, incorporating it, presumably, into organic phosphate complexes. As a result, the inorganic phosphate entering in the primary secretion diffuses back into the vitreous body so that a steady-state is established with a lower concentration in the aqueous humor and vitreous body than in the plasma. A similar state of affairs is probably present in the cerebrospinal system, the cerebrospinal fluid probably losing phosphate to the nervous tissue. As Friedmann & Levinson (98) have pointed out, the activity of the nervous tissue in determining the concentration of phosphate in the cerebrospinal fluid cannot be ignored, at any rate not in pathological conditions.

*Ascorbic Acid*

This vitamin has a high concentration in the aqueous humor. The degree of accumulation varies with the species, being some 15- to 20-fold in man, rabbit,

[23] In the ocular system it may frequently happen that fairly rapidly penetrating substances approach a steady state of less than unity; this steady state is only apparent, however, and results from diffusion into the lens and vitreous body (58, 155).

[24] Ross (189–191) has shown that insulin and growth-promoting hormone increase the rate of penetration of glucose into the aqueous humor; in alloxan diabetes the rate of penetration is very much reduced. Geiger *et al.* (99) have shown that the blood-brain barrier to glucose is strongly influenced by some normally circulating substance in the blood.

horse, ox and guinea pig (163, 174), and negligible in the cat and dog (174). The cerebrospinal fluid shows a small accumulation of the vitamin (38, 172, 173). The high concentration in the aqueous humor has been attributed to a synthesis of the vitamin by the lens (82, 127), but a variety of studies (35, 131, 143–145, 163) make it very unlikely that such a synthetic activity, if it occurs at all, will contribute appreciably to the maintenance of the high concentration in the aqueous humor. We are faced here with a definite active transport of material from the plasma to the aqueous humor.

*Sodium*

The concentration of this ion in the cerebrospinal or ocular fluid must exert a profound influence on the dynamics of fluid exchange, since it constitutes some 90 per cent of the cations in the plasma and fluids under consideration so that variations of small percentage magnitude will have relatively large effects on the total osmolar concentrations and thereby influence the relative osmotic pressures. In general, it would seem that the aqueous humor has a higher concentration of sodium than a dialysate of plasma (58, 60, 62, 63). In the cerebrospinal fluids of all the species that have been examined, the concentration of sodium is considerably larger than that in the aqueous humor, as table 6 shows. These facts would suggest that sodium is actively transported from the plasma into the primary secretion—aqueous humor or cerebrospinal fluid—as a result of the metabolic activity of the epithelial cells of the ciliary body or of the choroid plexus. Depending on the extent to which other substances are in excess or deficiency in the fluid, and on the extent to which sodium is accumulated, this active transport of sodium may lead to the formation of a fluid that is hypertonic in relation to the plasma. This would certainly appear to be true of the cerebrospinal fluid (68), but the degree of hypertonicity of the aqueous humor, if it exists, is probably very much smaller; in fact, it may well be that in some species, for example the rabbit and guinea pig, the fluid is hypotonic to plasma.[25] According to whether the fluid is hyper- or hypotonic to plasma, the fluid pressure will be influenced. Thus, other things being equal, the secretion of a hypertonic fluid will cause the fluid pressure to be high because of the influx of water across the blood-aqueous humor barrier. In this connection it is worth noting that a hypertonic cerebrospinal fluid would draw water away from the nervous tissue, if the extracellular fluid of this tissue had the same osmotic pressure as that of a dialysate of plasma. The possibility must not be ignored, however, that the extracellular fluid of the nervous tissue is maintained at a different degree of tonicity from that of a plasma dialysate by the secretory activity of the cells of the nervous tissue.[26]

*Chloride and Bicarbonate*

In the cerebrospinal fluid the concentration of chloride is some 20 per cent higher than in a dialysate of plasma; only to a small extent is this excess of chloride balanced by a deficiency of bicarbonate. Moreover, the excess of negative ions caused by this preponderance of chloride seems not to be completely balanced electrostatically by an equivalent excess of the identified positive ions, although the high concentration of sodium does contribute appreciably to this balance. It is possible that the cerebrospinal fluid contains some organic cation not present in the plasma. In the aqueous humor the state of affairs varies with the species. Large-eyed animals like the horse and goat have an excess of chloride and a deficiency of bicarbonate as in the cerebrospinal fluids of all species; in the rabbit and guinea pig the reverse is true (62, 63). In general, these variations in chloride and bicarbonate concentrations are not expressions of a tendency for the total chloride-plus-bicarbonate to re-

[25] For studies of the osmotic pressure of the fluid in relation to plasma the reader may be referred to the following papers: Gilman & Yudkin (100), Benham *et al.* (30), Roepke & Hetherington (187) and Kinsey (132) for the aqueous humor; Fremont-Smith *et al.* (94) and Blegen (37) for cerebrospinal fluid. The main difficulty in assessing the difference of osmotic pressure is to allow for any action of the plasma proteins. Davson & Purvis (68) measured the depression of freezing point of plasma, aqueous humor and cerebrospinal fluid from the same animal. By measuring the depression of freezing point of plasma and its dialysate they showed that the plasma proteins do, indeed, cause a speciously high depression of freezing point; on making allowance for this, it emerged that the aqueous humor of the rabbit was slightly hypotonic to plasma, while the cerebrospinal fluid was hypertonic to both fluids.

[26] If the concentration of sodium in the cerebrospinal fluid was greater than that in the extracellular fluid of the nervous tissue, we might expect to find significant differences in concentration between the fluid from the ventricles and from the spinal subarachnoid space; the latter, being more stagnant, would have a lower concentration than the former. The literature does not contain reliable measurements that would settle this point. In the monkey the author and his colleague, Dr. C. P. Luck, have been unable to find any significant differences in concentration of $Na^{21}$ in the fluid from the cisterna magna and lumbar sac 48 hr. after injection of the isotope.

TABLE 6. *Distribution of Sodium in Different Species*

[After Davson (58)]

| Species | $R_{Aq}$* | $R_{Cst}$† | $R_{Dial}$‡ |
|---|---|---|---|
| Horse | 0.935 | 0.97 | 0.925 |
| Ox | 0.94 | | |
| Sheep | 0.94 | | |
| Goat | 0.93 | | |
| Pig | 0.93 | | |
| Monkey | 0.97 | 1.01 | |
| Dog | 0.96 | 0.975 | 0.945 |
| Cat | 0.98 | 1.01 | 0.935 |
| Rabbit | 0.96 | 1.03 | 0.945 |
| Guinea pig | 0.98 | 1.04 | 0.955 |
| Rat | 0.99 | 1.03 | |

* Between aqueous humor and plasma; † between cerebrospinal fluid and plasma; ‡ between plasma dialyzate and plasma.

main constant since the excess of chloride in the aqueous humor of the horse, for example, is not by any means balanced by a corresponding deficiency in bicarbonate. In considering the relative concentrations of these two ions in aqueous humor it may well be that two separate factors must be borne in mind: *a*) the variation in the tonicity of the fluids among the different species and *b*) the variations in the buffering requirements of the intraocular contents among the different species.

If we regard the cerebrospinal fluid as the typical cavity-filling fluid, the absence of strong morphological differences in the cerebrospinal systems of the different mammalian species would lead us to expect to find, as we do indeed, only very small variations in the chemical composition of this fluid among the species. The shapes of the eyes of the different mammalian species, on the other hand, vary greatly, and we may imagine that the chemical composition of the primary cavity-filling fluid has undergone modifications to meet the new requirements imposed by these morphological variations. The aqueous humor of the small-eyed rabbit and guinea pig are those that have undergone the greatest modification, having lost entirely their excess of chloride and gained an excess of bicarbonate; the bicarbonate gained, however, is only about 50 per cent of the chloride lost when these are expressed in terms of equivalents per liter. The gain in bicarbonate may be regarded as a modification to meet the needs of the greater buffering requirements of the small eye; as figure 11 shows, the lens occupies an enormous percentage of the intraocular contents in these two eyes. We may ask, however, why the concentration of chloride has fallen so much. The low concentration of chloride is probably associated with a low tonicity of the fluid as a whole, and it may well be that in the small-eyed animals the prime physiological problem—apart from buffering—is the maintenance of a low intraocular pressure consistent with an adequate flow of fluid through the posterior and anterior chambers. Other things being equal, a hypotonic fluid would give a lower intraocular pressure than an isotonic or hypertonic one. Until more is known about the minute anatomy of the eyes of these species, it would be unwise to speculate as to why a small-eyed animal has to secrete a hypotonic aqueous humor to maintain its intraocular pressure within reasonable limits and large-eyed animals have to secrete a hypertonic fluid; and why, furthermore, all species secrete a hypertonic cerebrospinal fluid. As we shall see, the average level of the fluid pressure is determined by the rate of turnover of the fluid and the frictional resistance to drainage. If, in the large eyes and the cerebrospinal systems of all species, the frictional resistance is relatively low, while it is high in small eyes, the explanation emerges.[27]

## NTRACRANIAL AND INTRAOCULAR FLUID PRESSURES

### *General Considerations*

If a hypodermic needle is inserted into the anterior chamber of the eye or into the lumbar sac, fluid flows out of the needle; the pressure required just to prevent this outflow is the fluid pressure. The intraocular pressure is of the order of 20 mm Hg, while the cerebrospinal fluid pressure is considerably less, of the order of 150 mm $H_2O$ in man in the recumbent position. In both systems the fluids are enclosed, together with the blood in the arteries, veins and capillaries, in relatively indistensible coats. The pressure at any minute will be determined by a variety of factors which are by no means independent. The princi-

[27] It should be pointed out that the eyes of the rat, monkey and man are relatively small, yet their chloride and bicarbonate distribution ratios belong to those of the large-eyed animals. From the point of view of the lens/eye-weight ratio, however, man and the monkey are similar to the large-eyed animals. The rat stands out as an interesting exception, since its lens occupies a very large percentage of the eye weight; in this species, however, the rate of flow of aqueous humor is very rapid (62, 63), and it may be that the buffering is achieved by a more rapid turnover of fluid instead of by a higher concentration of bicarbonate.

pal factors are the arterial and venous pressures, the rate of secretion and the frictional resistance to drainage of the fluid. In the cerebrospinal system, moreover, gravitational factors have a marked significance. So far as the vascular system is concerned, we may expect fluctuations in the arterial pressure to have the smallest effects per se because the low distensibility of the arterial muscular coat reduces the amount of pressure that may be transmitted. Changes in the venous and capillary pressures, on the other hand, will have strong effects as regards both short-term and long-term influences. A rise in venous pressure causes the veins to dilate and thus transmit their increased pressure to the fluid; the high distensibility of the coats of the veins means, moreover, that most of the rise in pressure will be transmitted in this way. If the increased fluid pressures caused in this way led to a more rapid elimination of fluid, the effect of a rise in venous pressure would be transitory, the dilatation of the veins being compensated by a loss of fluid. However, a raised venous pressure might easily result in a diminished outflow of fluid since the latter has to drain into the venous system. In consequence, changes in venous pressure may be reflected in corresponding changes in fluid pressure that last as long as the changed venous pressure is maintained.

*Intraocular Pressure*

In experimental animals this is usually measured by a compensated manometer connected with a needle inserted in the anterior chamber.[28] The value so measured is usually given as about 25 mm Hg (150); but the trauma associated with insertion of the needle, and the general anesthesia employed, probably lead to erroneous results and it is doubtful whether absolute values of the intraocular pressure determined manometrically have much significance. For studies on man some form of 'tonometer' is employed; thus the impression tonometer of Schiotz measures, essentially, the extent to which a weighted plunger indents the cornea. By adequate calibration (95, 96) a reasonable estimate of the true intraocular pressure may be made; this would appear to be on the average some 18 to 19 mm Hg (96, 101, 216, 244). As recorded manometrically, the intraocular pressure shows pulses that are synchronous with the cardiac and respiratory cycles, the cardiac variation being of the order of 1 mm Hg and the respiratory variation rather more (248). Artificially induced variations in the general arterial pressure influence the intraocular pressure in the same sense, usually, but on a much smaller scale. To what extent they are directly transmitted effects from the intraocular arteries, and to what extent they are secondary consequences of changed venous and capillary pressures, is difficult to say. The fact that intravenous epinephrine may actually lower the intraocular pressure (248) in spite of an enormous rise in systemic arterial pressure emphasizes the importance of local, as opposed to general, vascular pressures. Thus the strong constriction of the arterioles lowers the venous pressure within and outside the eye so that the transmitted venous pressure is less and the ease of drainage is increased. Locally applied epinephrine may certainly lower the intraocular pressures, as Colle *et al.* (50) have shown, and it increases the visible drainage of aqueous humor in the aqueous veins (5, 6, 136). The action of amyl nitrite provides another example of the importance of local vascular pressures. On inhalation, this drug lowers the systemic arterial pressure; its vasodilator action, however, causes an increased venous pressure within and outside the eye, slowing drainage and increasing the transmitted venous pressure. The effect of the drug is consequently to raise the intraocular pressure (249).

Of some interest is the action of nitrogen mustard, applied locally. This drug causes a marked dilatation of the intraocular vessels; the blood-aqueous barrier is broken down and the intraocular pressure rises to enormous values (60 to 70 mm Hg). Here it is likely that the extreme vasodilatation is the most important factor, although the rapid exudation of fluid from the vessels of the iris and ciliary body is doubtless a contributory factor.[29]

There have been various studies on the modification of the intraocular pressure by osmotic means; theoretically, if the blood is suddenly made hypertonic, for example by the injection of 20 per cent sodium chloride, the fact that the blood-aqueous barrier is highly permeable to water but only slowly permeable to

[28] For various manometric methods employed, the reader may consult the classic paper of Wessely (248); more recent applications are those of Dayson & Purvis (67) employing an optical manometer, and of Guerry (118) employing an electromanometer.

[29] There are various drugs that may be classed with nitrogen mustard in this particular respect, raising the intraocular pressure and breaking down the blood-aqueous barrier; pilocarpine, physostigmine and diethylfluorophosphate may be cited, excellent histological and slit-lamp microscopical studies of their effects have been described by Larsson (139), von Sallmann & Dillon (225), Scholz (200), Cristini (53) and Poos (176, 178). Subconjunctival injection of hypertonic salts has essentially similar effects (248).

sodium and chloride ions must mean that water will pass rapidly out of the aqueous humor into the blood. Such effects have, indeed, been described (72, 121, 123); but the effects of hypertonic solutions are often so long-lasting that it seems quite certain that any osmotically induced changes are complicated by alterations in vascular tone that may lead to a prolonged fall in intraocular pressure (177).[30]

*Nervous Influences*

It is generally agreed that stimulation of the peripheral end of the cut cervical sympathetic nerve leads to a fall in the intraocular pressure (64, 114, 248); but in some animals, notably the cat and dog, the fall may be masked by the contraction of the smooth muscle of the orbit (114, 122, 248). Section of the sympathetic nerve has variable results; frequently it has no effect at all on the intraocular pressure, while on other occasions it may result in a considerable rise in the intraocular pressure (64). The effects of the sympathetic nerve are undoubtedly due to the constriction of the small vessels in the eye, causing a reduction in the capillary and venous pressures. Attempts to demonstrate a parasympathetic control over the intraocular pressure have generally failed. Stimulation of certain parts of the diencephalon would seem to lead to specific influences on the intraocular pressure (199, 226).

*Cerebrospinal Fluid Pressure*

In experimental animals this is measured by a cannula inserted into the cisterna magna. In man, the cannula is inserted into the lumbar sac with the subject usually in the lateral recumbent position. The pressures so recorded are considerably less than the intraocular pressure, being of the order of 150 mm saline, i.e. 11 mm Hg. [See Dixon & Halliburton (74), Becht (22), Bedford (26) and Goldensohn *et al.* (102) for experimental animals, and Masserman (152, 153) and Merritt & Fremont-Smith (158) for man.] The pressure exhibits cardiac and respiratory rhythms which were found by the usual methods of measurement to be of the order of only a few millimeters of saline in excursion. O'Connell (167) considered that these figures were grossly in error, owing to the damping that takes place during recording; and recently Goldensohn *et al.* (102) and Bering (33, 34) have shown that O'Connell was correct, the cardiac pulse, measured with a manometer with a minimum amount of inertia, being of the order of 50 mm saline (fig. 12). Removal of the choroid plexuses (32, 34) reduced very considerably the pulsations recorded from the ventricles so that it would seem that it is in this region of the vascular system that the arterial pulse is actually transmitted to the cerebrospinal fluid. As figure 12 shows, simultaneous recording from the ventricle, cisterna magna and lumbar sac indicates a progressive damping in the cerebrospinal system, the pulse pressures being 62, 49 and 29 mm saline in the respective locations.[31]

The effects of the vascular pressures on the cerebrospinal fluid pressure have been studied by Becht (22), Weed & Flexner (239) and Bedford (26, 27). In general, the venous pressure, measured in the sagittal sinus or torcular, seems to dominate the picture, some 60 per cent of any change in this pressure being transmitted to the cerebrospinal fluid. That the whole of the change in venous pressure is not transmitted is probably due partly to the circumstance that the elastic tension developed in the veins takes up some of the change, and partly to the circumstance that the venous pressure actually measured is that in the dural sinuses which is not necessarily the same as that in the cerebrospinal veins; it is these last that will transmit changes of pressure directly, while changes in the dural sinus pressure will influence the fluid pressure only by virtue of their effects on drainage. The effects of jugular occlusion which raises the cerebral venous pressure, and thus the fluid pressure, are not permanent (26), the fluid pressure returning to normal within 30 min., while the venous pressure remains high. Release of the jugular now causes a fall in fluid pressure below normal. The cerebrospinal system thus adapts itself to a raised intracranial venous pressure. It is unlikely that the adjustment consists in a more rapid drainage of fluid since, for this to occur, the drop in pressure between the cerebrospinal fluid and

[30] Injections of colloidal material, such as gum acacia or gelatin, are unlikely to have any significant effect on the relative osmotic pressures of plasma and aqueous humor; they may reduce the intraocular pressure, however. So far as gum acacia is concerned, this would appear to be due to the toxic action of this substance (15).

[31] Carmichael *et al.* (42) have analyzed the respiratory variation in some detail; the rise occurs during expiration and was earlier considered to be the result of the increased pressure in the great veins transmitted centrifugally. These authors showed this to be incorrect, the events in the cycle being more closely related with the fluctuations in the arterial pressure. Presumably the respiratory variations in arterial pressure are transmitted, by way of the capillaries and veins, to the cerebrospinal fluid; it is very questionable whether the changes in arterial pressure are directly transmitted, owing to the small distensibility of the arterial wall.


FIG. 12. Simultaneous ECG and pulse records from the cerebral ventricle, cisterna magna and lumbar subarachnoid space of an 11-year-old boy. The pulses, in millimeters of water, are: ventricular, 62; cisternal, 49; lumbar, 29. [From Bering (34).]

the dural sinuses must increase, an unlikely event with a raised venous pressure. Presumably some dislocation of fluid takes place, i.e., some of the cranial fluid passes into regions where the venous pressure has not been raised, namely into the spinal subarachnoid, room being made for it by an appropriate constriction of the veins in this region. That such readjustments are constantly being made during change in posture is very likely. Space does not permit a full discussion of the many interesting phenomena described and discussed by Weed & Flexner, Carmichael, Masserman and others on this particular aspect.[32] Suffice it to say that when the fluid pressure in man is recorded first in the lateral recumbent and then in the sitting positions, the pressure in the first posture is about 150 mm saline, while in the sitting position it is some 400 mm saline. The column of fluid that comes into play on sitting is some 675 mm saline, so that only about 40 per cent of the theoretically possible increase takes place. The system is, however, a closed one in the sense that an actual movement of fluid down the spinal subarachnoid space will be resisted by the fall in pressure that must occur if the space occupied by the fluid is not immediately filled. Thus, if a water-filled tube, sealed at the top, is raised to the vertical position, the fluid will not flow out because the atmospheric pressure will balance the height of the column. If the tube is open at the top the fluid will flow out of the tube because now the atmospheric pressure acts on the fluid in the tube. The state of affairs in the cerebrospinal system is something between these extremes, the system behaving as though the top of the tube were closed by an elastic cap; now the column of fluid becomes effective, but only partially, because the elastic tension in the cap resists the downward pull. If we transpose this picture to the cerebrospinal system, the elastic component becomes the extent to which the cranial vessels can expand to make room for the dislocation of cerebrospinal fluid from the ventricles and the cranial subarachnoid space. Similarly, when an animal is placed vertically, in the head-down position, the elastic component will be governed by the extent to which the spinal vessels can dilate. It is essentially the interplay between the distensibilities of the veins in the different regions of the central nervous system that determines the magnitude of the changes in cerebrospinal fluid pressure that result from changes in posture. In general, this interplay is such as to reduce very considerably the effects that might otherwise be expected when large columns of fluid suddenly are brought to bear.

That the vascular system reacts immediately to changes in the cerebrospinal fluid pressure is made very clear by the study of the effects of withdrawal or addition of fluid from or to the cerebrospinal system. Withdrawal of, say, 30 ml from man causes a rapid fall in fluid pressure followed by a fairly rapid return to normal; withdrawal of a further 30 ml has now a much more marked effect on the fluid pressure (152, 153). Evidently, the first loss was mainly compensated by an expansion of the blood vessels; such a process of compensation is, however, limited in extent so that a subsequent withdrawal produces a higher elastic reaction in the walls of the veins, and the compensatory

[32] The interested reader may be referred to the following papers: Weed *et al.* (240), Flexner *et al.* (84), Weed & Flexner (238), Flexner & Weed (85), Masserman (154) and von Storch *et al.* (228). The simple physical treatment of the problem, so enthusiastically pursued by Weed & Flexner who computed coefficients of meningeal elasticity, must be taken with a grain of salt. Pollock & Boshes (175) have blown a refreshing, if copious, blast of common sense on the purely mechanical aspects of the fluid pressure.

influx of blood produces a smaller rise in transmitted venous pressure.[33]

As with the ocular system, intravenous hypertonic solutions cause a profound fall in the cerebrospinal fluid pressure; but once again the effects are probably complicated by a direct influence of the hypertonic solutions on the vessels (89, 138, 154, 241–243). This consideration brings us to a word on the mechanical function of the cerebrospinal fluid in protecting the brain and spinal cord against the effects of sudden accelerations. The effect on the underlying brain of a blow on the skull by a stick, for example, is reduced by the cerebrospinal fluid, first, because of the loss of energy that occurs on transmitting the force from bone to water; second, because the force is spread over a larger area than the contact area between skull and stick, so that the pressure transmitted to the brain is smaller; finally, and most important, because the fluid may drain out of the skull or force blood to drain out, thereby making the system behave like a hydraulic buffer. In the same way, bending of the spine has no deleterious effects on the cord, compression being avoided by a similar buffering action. In fishes, where a true subarachnoid fluid is absent, the hydraulic buffer in the spine is replaced by a well developed perimeningeal layer of connective tissue lying between the primitive meninx and the periosteum.

[33] Other studies along these lines are those of Ayala (10), Ryder *et al.* (193), Foldes & Arrowood (87) and Haug (120).

## REFERENCES


1. Abelsdorff, G. and K. Wessely. *Arch. Augenheilk.* 64, Ergänzungsheft: 65, 1909.
2. Alexander, L. *Ztschr. ges. Anat. Abt. I Ztschr. Anat. u. Entwicklungsgeschichte* 95: 531, 1931.
3. Alexander, L., T. S. Jung and R. S. Lyman. *A. M. A. Arch. Neurol. & Psychiat.* 32: 1143, 1934.
4. Ascher, K. W. *Am. J. Ophth.* 25: 31, 1942.
5. Ascher, K. W. *Am. J. Ophth.* 25: 1174, 1942.
6. Ascher, K. W. *Am. J. Ophth.* 25: 1301, 1942.
7. Ascher, K. W. *A. M. A. Arch. Ophth.* 49: 438, 1953.
8. Ashton, N. *Brit. J. Ophth.* 35: 291, 1951.
9. Ashton, N. *Brit. J. Ophth.* 36: 265, 1952.
10. Ayala, G. *Monatsschr. Psychiat. u. Neurol.* 58: 65, 1925.
11. Bakay, L. *A. M. A. Arch. Neurol. & Psychiat.* 66: 419, 1951.
12. Bakay, L. *A. M. A. Arch. Neurol. & Psychiat.* 68: 629, 1952.
13. Bakay, L. *A. M. A. Arch. Neurol. & Psychiat.* 71: 673, 1954.
14. Bakay, L. and O. Lindberg. *Acta physiol. scandinav.* 17: 179, 1949.
15. Bárány, E. H. *Ophthalmologica* 116: 65, 1948.
16. Bárány, E. *Acta physiol. scandinav.* 22: 340, 1951.
17. Bárány, E. *A. M. A. Arch. Ophth.* 46: 326, 1951.
18. Bárány, E. *Modern Trends in Ophthalmology* (3rd series). London: Butterworth, 1955.
19. Bárány, E. and V. E. Kinsey. *Am. J. Ophth.* 32, Pt. 2: 177, 1949.
20. Barr, M. L. *Brain* 71: 281, 1948.
21. Baurmann, M. *Ber. deutsch. ophth. Gesellsch.* 48: 364, 1930.
22. Becht, F. C. *Am. J. Physiol.* 51: 1, 1920.
23. Becker, B., E. Linnér and E. H. Bárány. *A. M. A. Arch. Ophth.* 45: 653, 1951.
24. Becker, H. *Klin. Wchnschr.* 29: 706, 1951.
25. Becker, H. *Nervenarzt* 23: 146, 1952.
26. Bedford, T. H. B. *Brain* 58: 427, 1935.
27. Bedford, T. H. B. *Brain* 59: 324, 1936.
28. Bedford, T. H. B. *J. Physiol.* 128: 51P, 1955.
29. Behnsen, G. *Ztschr. Zellforsch. u. mikroskop. Anat.* 4: 515 1927.
30. Benham, G. H., W. S. Duke-Elder and T. H. Hodgson. *J. Physiol.* 92: 355, 1938.
31. Bering, E. A. *J. Neurosurg.* 9: 275, 1952.
32. Bering, E. A. *J. Neurosurg.* 11: 234, 1954.
33. Bering, E. A. *J. Neurosurg.* 12: 385, 1955.
34. Bering, E. A. *A. M. A. Arch. Neurol. & Psychiat.* 73: 165, 1955.
35. Bietti, G. and A. Carteni. *Boll. Soc. ital. biol. sper.* 9: 1066, 1934.
36. Blake, J. A. *J. Comp. Neurol.* 10: 79, 1900.
37. Blegen, E. *Skandinav. Arch. Physiol.* 81: 29, 1939.
38. Booij, J. *Rec. trav. chim.* 59: 713, 1940.
39. Borell, V. and Å. Örström. *Acta physiol. scandinav.* 10: 231, 1945.
40. Brierley, J. B. *J. Neurol. Neurosurg. & Psychiat.* 13: 203, 1950.
41. Brierley, J. B. and E. J. Field. *J. Anat.* 82: 153, 1948.
42. Carmichael, E. A., J. Doupe and D. J. Williams. *J. Physiol.* 91: 186, 1937.
43. Cestan, Riser and Laborde. *Rev. neurol.* 39: 353, 1923.
44. Christiansson, J. and E. Palm. *Acta ophth.* 32: 197, 1954.
45. Clara, M. *Das Nervensystem des Menschen* (2nd ed.). Leipzig: Barth, 1953.
46. Clark, W. E. LeGros. *J. Anat.* 55: 40, 1920.
47. Cockrill, J. R. *A. M. A. Arch. Neurol. & Psychiat.* 25: 1297, 1931.
48. Cohen, H. *Quart. J. Med.* 17: 289, 1923.
49. Cohen, H. *Quart. J. Med.* 20: 173, 1927.
50. Colle, J., P. M. Duke-Elder and W. S. Duke-Elder. *J. Physiol.* 71: 1, 1931.
51. Courtice, F. C. and W. J. Simmonds. *Australian J. Exper. Biol. & M. Sc.* 29: 255, 1951.
52. Cox, L. W., T. A. Chalmers and O. C. Ward. *Arch. Dis. Childhood* 27: 434, 1952.
53. Cristini, G. *Brit. J. Ophth.* 33: 228, 1949.

54. Cumings, J. N. and E. A. Carmichael. *Brain* 57: 338, 1934.
55. Dandy, W. E. *Ann. Surg.* 70: 129, 1919.
56. Dandy, W. E. and K. D. Blackfan. *Am. J. Dis. Child.* 8: 406, 1914.
57. Davson, H. *J. Physiol.* 128: 52P, 1955.
58. Davson, H. *J. Physiol.* 129: 111, 1955.
59. Davson, H. *Physiology of the Ocular and Cerebrospinal Fluids.* London: Churchill, 1956.
60. Davson, H., W. S. Duke-Elder and D. M. Maurice. *J. Physiol.* 109: 32, 1949.
61. Davson, H., W. S. Duke-Elder, D. M. Maurice, E. J. Ross and A. M. Woodin. *J. Physiol.* 108: 203, 1949.
62. Davson, H. and C. P. Luck. *J. Physiol.* 132: 454, 1956.
63. Davson, H. and C. P. Luck. *Am. J. Ophth.* 41: 809, 1956.
64. Davson, H. and P. A. Matchett. *J. Physiol.* 113: 387, 1951.
65. Davson, H. and P. A. Matchett. *J. Physiol.* 122: 11, 1953.
66. Davson, H., P. A. Matchett and J. R. E. Roberts. *J. Physiol.* 116: 47P, 1952.
67. Davson, H. and C. Purvis. *Brit. J. Ophth.* 34: 351, 1950.
68. Davson, H. and C. Purvis. *J. Physiol.* 124: 12P, 1954.
69. Davson, H. and C. B. Weld. *Am. J. Physiol.* 134: 1, 1941.
70. De Haan, J. and S. van Creveld. *Biochem. Ztschr.* 123: 190, 1921.
71. De Haan, J. and S. van Creveld. *Biochem. Ztschr.* 124: 172, 1921.
72. Dieter, W. *Arch. Augenheilk.* 96: 179, 1925.
73. Dixon, W. E. and W. D. Halliburton. *J. Physiol.* 47: 215, 1913.
74. Dixon, W. E. and W. D. Halliburton. *J. Physiol.* 48: 128, 1914.
75. Duke-Elder, W. S. *Brit. J. Ophth.* 10: 513, 1926.
76. Duke-Elder, W. S. *A Textbook of Ophthalmology.* London: Kimpton, 1932, vol. 1.
77. Eichler, O. and F. Linder. *Klin. Wchnschr.* 29: 9, 1951.
78. Eichler, O., F. Linder and K. Schmeiser. *Klin. Wchnschr.* 29: 707, 1951.
79. Esser, H. and F. Heinzler. *Deutsche med. Wchnschr.* 77: 1329, 1952.
80. Esser, H., F. Heinzler and H. Pau. *von Graefes Arch. Ophth.* 155: 11, 1954.
81. Essick, C. R. *Contr. Embryol. Carnegie Inst.* 9: 377, 1920.
82. Fischer, F. P. *Arch. Augenheilk.* 108: 527, 1934.
83. Flexner, L. B. *Am. J. Physiol.* 106: 201, 1933.
84. Flexner, L. B., J. H. Clark and L. H. Weed. *Am. J. Physiol.* 101: 292, 1932.
85. Flexner, L. B. and L. H. Weed. *Am. J. Physiol.* 104: 681, 1933.
86. Flexner, L. B. and H. Winters. *Am. J. Physiol.* 101: 697, 1932.
87. Foldes, F. F. and J. G. Arrowood. *J. Clin. Invest.* 27: 346, 1948.
88. Forbes, H. S. and S. Cobb. *A. Res. Nerv. & Ment. Dis., Proc.* 18: 201, 1938.
89. Forbes, H. S. and G. I. Nason. *A.M.A. Arch. Neurol. & Psychiat.* 34: 533, 1935.
90. François, J., A. Neetens and J. M. Collette. *Brit. J. Ophth.* 39: 220, 1955.
91. Frazier, C. H. and M. M. Peet. *Am. J. Physiol.* 35: 268, 1914.
92. Freeman, W., H. H. Schoenfeld and C. Moore. *J.A.M.A.* 106: 96, 1936.
93. Fremont-Smith, F., M. E. Dailey, H. H. Merritt and M. P. Carroll. *A.M.A. Arch. Neurol. & Psychiat.* 25: 1290, 1931.
94. Fremont-Smith, F., G. W. Thomas, M. E. Dailey and M. P. Carroll. *Brain* 54: 303, 1931.
95. Friedenwald, J. S. *Am. J. Ophth.* 20: 985, 1937.
96. Friedenwald, J. S. *Am. J. Ophth.* 31: 935, 1948.
97. Friedenwald, J. S. and B. Becker. *A.M.A. Arch. Ophth.* 54: 799, 1955.
98. Friedman, A. and A. Levinson. *A.M.A. Arch. Neurol. & Psychiat.* 74: 424, 1955.
99. Geiger, A., J. Magnes, R. M. Taylor and M. Veralli. *Am. J. Physiol.* 177: 138, 1954.
100. Gilman, A. and A. M. Yudkin. *Am. J. Physiol.* 104: 235, 1933.
101. Glees, M. *von Graefes Arch. Ophth.* 153: 356, 1952.
102. Goldensohn, E. S., R. W. Whitehead, T. M. Parry, J. H. Spencer, R. F. Grover and W. B. Draper. *Am. J. Physiol.* 165: 334, 1951.
103. Goldmann, E. E. *Beitr. klin. Chir.* 64: 192, 1909.
104. Goldmann, E. E. *Abhandl. preuss. Akad. Wiss. Phys.-Math. Kl.* No. 1, 1913.
105. Goldmann, H. *Ophthalmologica* 111: 146, 1946.
106. Goldmann, H. *Ophthalmologica* 112: 344, 1946.
107. Goldmann, H. *Ophthalmologica* 114: 81, 1947.
108. Goldmann, H. *Ophthalmologica* 116: 195, 1948.
109. Goldmann, H. *Ophthalmologica* 117: 240, 1949.
110. Goldmann, H. *Ophthalmologica* 119: 65, 1950.
111. Golomann, H. *Docum. ophth.* V–VI: 278, 1951.
112. Grant, W. M. *A.M.A. Arch. Ophth.* 44: 204, 1950.
113. Grant, W. M. *A.M.A. Arch. Ophth.* 54: 245, 1955.
114. Greaves, D. P. and E. S. Perkins. *Brit. J. Ophth.* 36: 258, 1952.
115. Greef, R. *Arch. Augenheilk.* 28: 178, 1894.
116. Greenberg, D. M., R. E. Aird, M. D. D. Boelter, W. W. Campbell, W. E. Cohen and M. M. Murayama. *Am. J. Physiol.* 140: 47, 1943.
117. Gruner, J., S. S. Sung, M. Tubiana and J. Segarra. *Compt. rend. Soc. de biol.* 145: 203, 1951.
118. Guerry, D. *Tr. Am. Ophth. Soc.* 49: 525, 1951.
119. Harris, J. E. and L. B. Gehrsitz. *Am. J. Ophth.* 32, Pt. 2: 167, 1949.
120. Haug, K. *Arch. Psychiat.* 97: 303, 1932.
121. Haupt, W. *Arch. Augenheilk.* 78: 359, 1915.
122. Henderson, E. E. and E. H. Starling. *J. Physiol.* 31: 305, 1904.
123. Hertel, E. *von Graefes Arch. Ophth.* 88: 197, 1914.
124. Huggert, A. *Acta ophth.* 33: 271, 1955.
125. Huggert, A., A. Holmberg and A. Esklund. *Acta opth.* 33: 429, 1955.
126. Hunter, G., M. V. Smith and L. M. Taylor. *Biochem. J.* 56: 588, 1954.
127. Huysmans, J. H. B. M. and F. P. Fischer. *Ophthalmologica* 103: 21, 1942.
128. Järvi, O. *Acta Soc. Med. "Duodecim"* (series A) 23: 84, 1940.
129. Kabat, E. A., D. H. Moore and H. Landow. *J. Clin. Invest.* 21: 571, 1942.
130. Key, A. and G. Retzius. *Anatomie des Nervensystems und des Bindegewebes.* Stockholm: Samson and Wallin, 1876.
131. Kinsey, V. E. *Am. J. Ophth.* 30: 1262, 1947.

132. Kinsey, V. E. *J. Gen. Physiol.* 34: 389, 1951.
133. Kinsey, V. E. and E. Bárány. *Am. J. Ophth.* 32: 189, 1949.
134. Kinsey, V. E. and E. Palm. *A.M.A. Arch. Ophth.* 53: 330, 1955.
135. Kleinert, H. *Klin. Monatsbl. Augenh.* 122: 665, 1953.
136. Kleinert, H. *von Graefes Arch. Ophth.* 157: 24, 1955.
137. Kral, A., Z. Stary and R. Winternitz. *Ztschr. ges. Neurol. Psychiat.* 122: 308, 1929.
138. Kubie, L. S. and D. M. Hetler. *A.M.A. Arch. Neurol. & Psychiat.* 20: 749, 1928.
139. Larsson, S. *Ann. ocul.* 169: 94, 1932.
140. Lauber, H. *Arb. anat. Inst. Wiesbaden* 18: 371, 1902.
141. Lindberg, B. and L. Ernster. *Biochem. J.* 46: 43, 1950.
142. Linder, G. C. and E. A. Carmichael. *Biochem. J.* 22: 46, 1928.
143. Linnér, E. *Acta physiol. scandinav.* 26: 57, 1952.
144. Linnér, E. *Acta physiol. scandinav.* 26: 70, 1952.
145. Linnér, E. *Acta physiol. scandinav.* 26: 130, 1952.
146. Linnér, E., C. Rickenbach and H. Werner. *Acta opth.* 28: 469, 1950.
147. Lowenthal, A. *Acta neurol. et psychiat. belg.* 54: 192, 1954.
148. Macklin, C. F. and M. T. Macklin. *A.M.A. Arch. Neurol. & Psychiat.* 3: 353, 1920.
149. Maggiore, L. *Ann. ottal. e clin. ocul.* 40: 317, 1917.
150. Magitot, A. *Ann. ocul.* 154: 272, 1917.
151. Mandelstamm, M. and L. Krylow. *Ztschr. ges. exper. Med.* 60: 63, 1928.
152. Masserman, J. H. *A.M.A. Arch. Neurol. & Psychiat.* 32: 523, 1934.
153. Masserman, J. H. *J.A.M.A.* 102: 2084, 1934.
154. Masserman, J. H. *J. Comp. Neurol.* 61: 543, 1935.
155. Maurice, D. *J. Physiol.* 112: 367, 1951.
156. McCance, R. A. and E. Watchorn. *Quart. J. Med.* 24: 371, 1931.
157. Meek, W. J. *J. Comp. Neurol.* 17: 286, 1907.
158. Merritt, H. H. and F. Fremont-Smith. *The Cerebrospinal Fluid.* Philadelphia: Saunders, 1937.
159. Mestrezat, W. *Le Liquide Céphalo-Rachidien Normal et Pathologique* (Thèse). Montpellier: Université de Montpellier, 1911.
160. Moore, E., H. G. Scheie and F. H. Adler. *A.M.A. Arch. Ophth.* 27: 317, 1942.
161. Moses, R. A. and M. Bruno. *Am. J. Ophth.* 33: 389, 1950.
162. Mott, F. W. *Lancet* 179: 1, 1910.
163. Müller, H. K. and W. Buschke. *Arch. Augenheilk.* 108: 368, 1934.
164. Munich, W. *von Graefes Arch. Ophth.* 154: 50, 1953.
165. Niedermeier, S. *Klin. Monatsbl. Augenh.* 120: 644, 1952.
166. Nobécourt, P. and R. Voisin. *Arch. gen. de méd.* 192: 3018, 1903.
167. O'Connell, J. E. A. *Brain* 66: 204, 1943.
168. Palm, E. *Acta ophth.* 25: 139, 1947.
169. Patek, P. R. *Anat. Rec.* 88: 1, 1944.
170 Perkins, E. S. *Brit. J. Ophth.* 39: 215, 1955.
171. Pettit, A. and J. Girard. *Arch. anat. micr., Paris* 5: 213, 1902.
172. Plaut, F. and M. Bülow. *Hoppe-Seyler's Ztschr. physiol. Chem.* 236: 241, 1935.
173. Plaut, F. and M. Bülow. *Ztschr. ges. Neurol. Psychiat.* 153: 182, 1935.
174. Podestà, H. H. and J. Baucke. *von Graefes Arch. Ophth.* 139: 720, 1938.
175. Pollock, L. J. and B. Boshes. *A.M.A. Arch. Neurol. & Psychiat.* 36: 931, 1936.
176. Poos, F. *von Graefes Arch. Ophth.* 127: 489, 1931.
177. Poos, F. *Klin. Monatsbl. Augenh.* 89: 145, 1932.
178. Poos, F. *Arch. Augenheilk.* 110: 499, 1937.
179. Putnam, T. J. *Bull. Johns Hopkins Hosp.* 33: 181, 1922.
180. Radovici, A., I. Bazgan and O. Meller. *Compt. rend. Soc. de biol.* 114: 207, 1933.
181. Ragazzini, F. *Riv. clin. pediat.* 50: 381, 1952.
182. Rasmussen, A. T. *The Principal Nervous Pathways* (4th ed.). New York: Macmillan, 1952.
183. Redaelli, P. and A. Previtera. *Riv. pat. nerv.* 44: 601, 1934.
184. Riser. *Le Liquide Céphalo-Rachidien.* Paris: Masson, 1929.
185. Roeder, F. *$^{32}P$ im Nervensystem. Der Phosphataustausch des Nervensystems untersucht mit Hilfe der Isotopenmethode.* Göttingen: Muster-Schmidt, 1948.
186. Roeder, F. and O. Rehm. *Die Cerebrospinalflüssigheit.* Berlin: Springer, 1942.
187. Roepke, R. R. and W. A. Hetherington. *Am. J. Physiol.* 130: 340, 1940.
188. Rohen, J. *Ber. deutsch. ophth. Gesellsch.* 58: 65, 1953.
189. Ross, E. J. *Brit. J. Ophth.* 36: 41, 1952.
190. Ross, E. J. *J. Physiol.* 116: 414, 1952.
191. Ross, E. J. *J. Physiol.* 127: 247, 1955.
192. Rossi, G. and G. Schneider. *Klin. Wchnschr.* 31: 969, 1953.
193. Ryder, H. W., F. F. Espey, F. D. Kimbell, E. J. Penka, A. Rosenauer, A. Podolsky and J. P. Evans. *J. Lab. & Clin. Med.* 41: 428, 1953.
194. Sachs, E., H. Wilkins and C. F. Sams. *A.M.A. Arch. Neurol. & Psychiat.* 23: 130, 1930.
195. Sachs, J. and G. G. Culbreth. *Am. J. Physiol.* 163: 746P, 1950.
196. Schaltenbrand, G. and T. Putnam. *Deutsche Ztschr. Nervenh.* 96: 123, 1927.
197. Scheid, K. F. and L. Scheid. *Arch. Psychiat.* 117: 219, 1944.
198. Scheid, K. F. and L. Scheid. *Arch. Psychiat.* 117: 641, 1944.
199. Schmerl, E. and B. Steinberg. *Am. J. Ophth.* 33: 1379, 1950.
200. Scholz, R. O. *J. Pharmacol.* 88: 23, 1946.
201. Scholz, R. O., W. S. Cowie and W. S. Wilde. *Am. J. Ophth.* 30: 1516, 1947.
202. Scholz, R. O. and E. M. Ralston. *Anat. Rec.* 75: 365, 1939.
203. Schulemann, W. *Arch. mikroskop. Anat.* 79: 223, 1912.
204. Schurr, P. H., R. L. McLaurin and F. D. Ingraham. *J. Neurosurg.* 10: 515, 1953.
205. Seidel, E. *von Graefes Arch. Ophth.* 95: 1, 1918.
206. Seidel, E. *von Graefes Arch. Ophth.* 104: 357, 1921.
207. Seidel, E. *von Graefes Arch. Ophth.* 112: 252, 1923.
208. Simmonds, W. J. *Australian J. Exper. Biol. & M. Sc.* 30: 261, 1952.
209. Simmonds, W. J. *Australian J. Exper. Biol. & M. Sc.* 31: 77, 1953.
210. Solomon, H. C., L. J. Thompson and H. M. Pfeiffer. *J.A.M.A.* 79: 1014, 1922.
211. Stary, Z. and R. Winternitz. *Arch. Augenheilk.* 108: 433, 1934.

212. Stern, L. and R. Gautier. *Arch. internat. Physiol.* 17: 138, 1921.
213. Stern, L. and R. Gautier. *Arch. internat. Physiol.* 17: 391, 1922.
214. Stern, L. and R. Gautier. *Arch. internat. Physiol.* 20: 403, 1923.
215. Stuck, R. M. and D. L. Reeves. *A.M.A. Arch. Neurol. & Psychiat.* 40: 86, 1938.
216. Suda, K. and Y. Kiritoshi. *Acta Soc. ophth. jap.* 57: 886, 1953.
217. Sundwall, J. *Anat. Rec.* 12: 221, 1917.
218. Sweet, W. H. and H. B. Locksley. *Proc. Soc. Exper. Biol. & Med.* 84: 387, 1953.
219. Sweet, W. H., B. Selverstone, S. Solloway and D. Stetten. *American College of Surgeons Surgical Forum.* Philadelphia: Saunders, 1950, p. 376.
220. Sweet, W. H., B. Selverstone, A. Solomon and L. Bakay. *J. Clin. Invest.* 28: 814, 1949.
221. Thomassen, T. L. *Acta ophth.* 28: 479, 1950.
222. Tron, E. *von Graefes Arch. Ophth.* 119: 659, 1928.
223. Tschirgi, R. D. *Am. J. Physiol.* 163: 765P, 1950.
224. Tubiana, M., P. Benda and J. Constans. *Rev. neurol.* 85: 17, 1951.
225. von Sallmann, L. and B. Dillon. *Am. J. Ophth.* 30: 1244, 1947.
226. von Sallmann, L. and O. Lowenstein. *Am. J. Ophth.* 39, Pt. 1: 11, 1955.
227. von Sallmann, L. and D. H. Moore. *A.M.A. Arch. Ophth.* 40: 279, 1948.
228. von Storch, T. J. C., E. A. Carmichael and T. E. Banks. *A.M.A. Arch. Neurol. & Psychiat.* 38: 1159, 1937.
229. Vrabec, F. *Ophthalmologica* 123: 20, 1952.
230. Wallace, G. B. and B. B. Brodie. *J. Pharmacol.* 65: 220, 1939.
231. Walter, F. K. *Die Blut-Liquorschranke. Eine physiologische und klinische Studie.* Leipzig: Thieme, 1929.
232. Wang, J. *J. Gen. Physiol.* 31: 259, 1948.
233. Weed, L. H. *J. Med. Research* 31: 51, 1914.
234. Weed, L. H. *Contr. Embryol. Carnegie Inst.* 9: 425, 1920.
235. Weed, L. H. *Am. J. Anat.* 31: 191, 1923.
236. Weed, L. H. *J. Am. Physiol.* 114: 40, 1935.
237. Weed, L. H. and H. Cushing. *Am. J. Physiol.* 36: 77, 1915.
238. Weed, L. H. and L. B. Flexner. *Am. J. Physiol.* 101: 668, 1932.
239. Weed, L. H. and L. B. Flexner. *Am. J. Physiol.* 105: 266, 1933.
240. Weed, L. H., L. B. Flexner and J. H. Clark. *Am. J. Physiol.* 100: 246, 1932.
241. Weed, L. H. and W. Hughson. *Am. J. Physiol.* 58: 53, 1921.
242. Weed, L. H. and W. Hughson. *Am. J. Physiol.* 58: 85, 1921.
243. Weed, L. H. and W. Hughson. *Am. J. Physiol.* 58: 101, 1921.
244. Weekers, R., M. Watillon and M. De Rudder. *Ann. ocul.* 188: 920, 1955.
245. Weinstein, P. *Brit. J. Ophth.* 34: 161, 1950.
246. Weinstein, P. and J. Forgács. *Am. J. Ophth.* 38: 377, 1954.
247. Wessely, K. *von Graefes Arch. Ophth.* 50: 123, 1900.
248. Wessely, K. *Arch. Augenheilk.* 60: 1, 1908.
249. Wessely, K. *Arch. Augenheilk.* 78: 247, 1915.
250. Wislocki, G. B. and L. S. King. *Am. J. Anat.* 58: 421, 1936.
251. Wislocki, G. B. and T. J. Putnam. *Anat. Rec.* 19: 281, 1920.
252. Witmer, R. *Ophthalmologica* 123: 280, 1952.
253. Wolff, E. *Anatomy of the Eye and Orbit.* London: Lewis, 1954.
254. Wolfrum, M. In: *Graefe-Sämische Handbuch der Augenheilkunde,* edited by T. Axenfeld and A. Elschnig. Berlin: Springer, 1931, vol. 1, pt. 2, p. 218.
255. Woollam, D. H. M. and J. W. Millen. *Biol. Rev.* 29: 251, 1954.
256. Woollam, D. H. M. and J. W. Millen. *J. Anat.* 89: 193, 1955.
257. Woollard, H. H. *J. Anat.* 58: 89, 1924.
258. Wright, S. L., E. F. Herr and J. R. Paul. *J. Clin. Invest.* 9: 443, 1930.
259. Zwiauer, A., H. Borschein and E. Deutsch. *Am. J. Ophth.* 34: 1403, 1951.

CHAPTER LXXIII

# Neural metabolism and function—introduction

SIR RUDOLPH A. PETERS | *A. R. C. Institute of Animal Physiology, Babraham, Cambridge, England*

IT IS DIFFICULT TO BE PATIENT; and when this patience must extend past a lifetime, it becomes almost humanly impossible not to hope for some quicker result. This is possibly the reason why there has been in the past such reluctance to encourage the works of those who sat down patiently to unravel the intricate chemistry and biochemistry of the nervous system. The isolated vision of the pioneer J. L. W. Thudichum[1] becomes more remarkable the more we study it; few could attain to the faith which made him write: "Premiums in the shape of sensational discoveries may be hoped for but cannot be assured even to the greatest genius." And again: "But what has to penetrate in relation to this question, more completely into the consciousness of pathologists is this, that to understand zymoses, to be able to counteract them by rational as distinguished from empirical or accidentally discovered means, is only possible by the aid of a complete knowledge of the chemical constitution of all the tissues, organs and juices of the body and of all their possible decomposition products." Very much later than Thudichum, Irvine Page quotes a statement made to him by a distinguished neurologist in London who dismissed brain chemistry "with the remark that nothing would ever be learnt by the analysis of a cerebral hash." In a way the very success of histology in delineating the complex microstructure of nervous tissues and of demonstrating changes occurring in disease stood in the light of the recognition that prior to the visible microscopic lesion there must be a change in the biochemistry, a biochemical lesion, if one likes to term it so, which initiates the changes ultimately registering to the microscope as difference in staining and structure. Even today in many quarters this view is little understood. To put it crudely, in regard to the nervous system we are much in the position of someone trying to repair a motor without knowing anything about its anatomy. To carry this analogy a step further, it might really be some help to fragment the motor by gentle methods and so try to find out what individual parts such as the carburetor or spark plug could do. The analogy cannot be pressed too far, but those who think that guess work as to this or that possible constituent playing its part in some disease can produce results without real knowledge of the dynamic working machinery are not so far removed from our friend, ignorant of his car engine. The only great difference is the enormously greater complexity of the brain and nerves, and this is where our admiration of Thudichum must come in. Nearly 100 years ago he had the cool courage to settle down and dissect the complexities of the organic chemistry of mixtures of substances, many of which can be completely understood only by modern methods.

After Thudichum, little happened for many years, although the Kochs made their valuable studies of myelination in relation to development. There had to be a gap until the modern approach developed through enzyme studies in relation to the glycolytic and oxidation fields, mainly in the United Kingdom and in the U. S. A. These led to the generalization that it was the carbohydrates which were the fuel for nervous activity, and to the connection of this with some vitamins, especially thiamine in its relation to convulsive activity. Much of this work in the late 1920's and early 1930's was done with crude brei and without the knowledge and refinements of modern methods, but it did reap a rich harvest. We

[1] Thudichum's work appeared in two books: *A Treatise on the Chemical Construction of the Brain*. London: Bailliere, Tindall and Cox, 1884; and *Die chemische Konstitution des Gehirns des Menschen und der Tiere*. Tübingen: Pietzcker, 1901.

may instance the knowledge of the part played by pyruvic acid, which has now led to clinical tests in the blood for beri beri and other conditions. Much of this work, however, has now passed into history, and there is an increasing interest in the whole field of lipids and their dynamic interchanges. At the same time, the progress of pharmacology has given us substances of great activity when presented to nervous tissue in minute amounts; we may mention 5-hydroxytryptamine. More important still, the writer feels, is the development of micromethods of enzyme analysis in Chicago by Lowry where pioneer studies in micromethods of the Copenhagen school led by Linderstrøm-Lang are being applied to the nervous system. When these can be combined adequately with electron microscope pictures, we may then be able to start upon our final analysis of events. Already we know that there is a pharmacological connection between activity and the events concerned with acetylcholine. Further, it is clear from some of the work with vitamin-B deficiencies and with toxic substances that the background enzyme activity can be rather directly related to convulsive states. At the same time we must not expect that studies *in vitro* can give us the final and predominantly important subtleties which must depend upon the whole intact tissues with their full organization. Indeed, as the contents of this book show, it is still not possible to pick up experimentally metabolic changes accompanying mental activity. The central nervous system too is additionally protected against changes in its external chemical environment by the so-called blood-brain barrier.

In a survey of what lies before us, it may be that we ought to follow the example of the astronomers who for some 150 years have been planning ahead for their successors. The time scale of their events and the cost of their equipment doubtless made this necessary. In our case it is true that new techniques are continually arising and that this would mean a constant revision of any scheme; but at the same time, some degree of international planning which was not restrictive might help some phases of the work. The sheer economics of mental illness almost imposes exploration of every possible approach. In any case the note of patience must be sounded again. It will take time to understand it all properly from whatever angle the approach is made; but it can be predicted with complete confidence that when we do, the practical applications in medicine will follow rapidly, and that even partial solutions will be better than empiricism.

This volume of essays on various aspects of the modern picture must therefore be regarded as a volume of milestones in our approach to the final goal of an understanding of neurophysiology interpreted in the widest sense. To those in the 'trenches' of medicine much of it must seem to be remote, and indeed much will be superseded with newer observations; but even if 10 per cent remain, it is a truism to point out that this is an important advance in knowledge. The Editors have arranged so that the subject is well covered. The chemical background is given attention in neural chemistry and metabolism, and the more dynamic aspects in neuronal metabolism. A large amount of strictly biochemical work *in vitro* is well reviewed in central nervous system metabolism *in vitro*, and the same extensions of this *in vivo* are then set forth. To complete the picture, separate chapters have been devoted to the effect on neural function of changes in cellular metabolism and then to abnormalities induced by the presence of either nutritional deficiencies or of congenital disorders. One should underline here the astonishing brain disturbances induced by thiamine deficiency and in the pellagra induced by nicotinic acid deficiency. They are not so surprising when we remember the general sloth and hallucinations which occur in hypothyroidism, or the effects of hypoglycemia following the overdose of insulin. It is still not clear why glucose is almost unique in stopping insulin convulsions. Perhaps this is related to recent work in Rome upon the increase in glycogen concentration in rat diaphragms induced by insulin.

The Editors had in mind a contribution to the understanding of the relations between metabolism and function, questions of the most far-reaching importance because they involve a decision as to the extent to which the metabolism only maintains the structure and the extent to which it contributes to the working functions. The writer thinks that a perusal should convince us that it is now no longer advisable to take the view of some older physiologists that one can separate the point of view of the biochemists and the physiologists. According to this (and it was reasonable at the time), physiologists could accept the idea of the central nervous system as a normal working system, relegating the constitution of the substances being investigated largely to the role of excretion and other such biochemical processes. At least it must be clear now that the biochemistry does and must often actively intrude even in physiological experiments. In this region of metabolism we are beginning to see some connection between

physiological knowledge taken in its widest sense and its clinical effects, although problems such as that of hunger, as well as 'crucially' that of mental activity, still elude us. Again we want very much some way of repairing brain damage by the growth of new cells; but such ideas are indeed a commonplace.

In appraising the present contributions to be found in a modern *Section on Neurophysiology*, it is hard to avoid some emphasis on the practical aspects of advances in the field. Yet in doing this it is wrong to lose sight of the scientific interest and one might almost say privilege of being able to study that very organ associated with the intellect upon whose accurate functioning these penetrations into the laws of nature rest. Evolution has produced somehow a tissue where the burden and excitement of thought become interconnected. Whichever way we look at it, whether we believe in dualism or not, thoughts which ultimately find their expression in action, muscular or otherwise, certainly impinge at one stage on some brain cell in a way that generates the response upon which intellectual and muscular effort depend. The quest of knowledge here for its own sake has some transcendental value.

CHAPTER LXXIV

# Chemical architecture of the central nervous system

DONALD B. TOWER *National Institute of Neurological Diseases and Blindness, Bethesda, Maryland*

CHAPTER CONTENTS



THE GENERAL CHEMICAL MAKE-UP of the central nervous system has been known for well over a century, but the details of its composition and particularly of its organization are still far from complete. The difficulty has been in part due to the nature of the components of neural tissues for which suitable analytical approaches have only recently been developed. There is a more fundamental difficulty related to the nonhomogeneous nature of the nervous system both in its organization and in its function.

The division of the brain and spinal cord into gray and white matter is convenient both structurally and functionally, and it has been estimated that the two portions are approximately equal in volume (gray 45 per cent, white 55 per cent of the total) (223). Yet myelinated fibers are prominent in certain gray areas, notably in the cerebral cortex and thalamus; and in certain species, like the whale, neurons are present deep in white matter (225). Even if this division is accepted as a general approximation, each portion is not homogeneous within itself. While this is strictly true for most organs of the body, compared to the liver, for example, the brain is much less so. This is partly due to the variety of cell types, an example of which is summarized in table 1 based on studies of the rat (158, 177); similar data have been reported for other species (2, 88, 99, 191). Thus, in gray areas, neurons comprise only about 20 per cent of the total cell population, the remainder including four other cell types which contribute to both structure and function. A similar situation exists in white matter and it is noteworthy that the total cell population here approaches that for cerebral cortex. The cerebellar cortex on the other hand has many more cells than either of the foregoing. Looking at another aspect of this situation, the cell bodies of neurons in cerebral cortex occupy only about 5 per cent of the total volume (146, 207), yet their dendrites and axons ramify throughout many layers and areas, representing a vastly greater cytoplasmic volume (some 25 per cent of the cortical total) than that of the perikaryon. Pope (179) has discussed some of the problems which these features pose for neurochemical studies.

Although the gross composition and, in some instances, the finer composition of gray and white areas, respectively, are similar, they are very different from many physiological and biochemical standpoints. It would seem that such differences should be reflected in the structural chemical organization of the individual areas. This may be so, but the elucidation of such differences has not yet been achieved.

The foregoing sets forth some of the basic problems which must be borne in mind during consideration of the material to follow. This chapter is not intended to be a detailed review of the subject since these are available elsewhere (153, 168, 194). Detailed consideration of species differences cannot be presented

TABLE 1. *Distribution of Cell Types in Rat Cerebral Tissues**

| Sample | Total Cells | Neurons | Glia† | Endothelial Cells |
|---|---|---|---|---|
| Mixed cerebral cortex | 9.6 | 2.3 | 5.8 | 1.6 |
| Corpus callosum (white) | 7.8 | 0 | 7.6 | 0.2 |
| Cerebellar cortex | 47.7 | | | |

* Numbers of cells $\times 10^7$ per gm weight, according to data of Nurnberger (158) and of Pope (177).

† Percentage of glial types:

| | Astrocytes | Oligodendroglia | Microglia |
|---|---|---|---|
| Gray matter | 40 | 52 | 8 |
| White matter | 30 | 65 | 5 |

because the available data are too scattered and incomplete. And embryological and developmental aspects would seem to be beyond the scope of this chapter, but may be obtained from several good sources (65, 242). It has seemed more important to attempt to indicate how the basic components are organized into a functioning tissue fabric. At best, the separation of structure from function is an artificial convenience; but, since the details of metabolism and function are covered in succeeding chapters, the latter will not be stressed here. It must be remembered, however, that the framework of neural tissues is not simply a static support but is in actuality composed to a large degree of the lipid and protein moieties of enzyme systems which are the sites of metabolic activity and the loci for conduction and transmission potentialities.

## COMPOSITION OF THE CENTRAL NERVOUS SYSTEM

### *Macrochemical Data*

The first chemical fact ascertained about the brain was a report by Hensing in 1719 (101) of its prominent phosphate content. By 1811 when the first analysis of human and animal brain was published by Vauquelin (236), investigators had a surprisingly good concept of its composition. Vauquelin reported the following composition for whole brain (236, p. 232):

| | 80 centièmes |
|---|---|
| 1.° Eau, environ | 4 53 |
| 2.° Matière grasse blanche | 70 |
| 3.° Matière grasse rougeâtre | 7 |
| 4.° Albumine | 1 12 |
| 5.° Osmazome | 1 50 |
| 6.° Phosphore | 5 15 |
| 7.° Acide, sels, soufre | |
| | 100 00 |

The lipid percentage is low, since Vauquelin employed only alcohol as extractant, but the protein (*albumine*) and water are comparable to present analyses. Among the salts, Vauquelin recognized the presence of potassium, calcium and magnesium plus a little sodium chloride. He also reported the higher lipid content of brain stem and spinal cord, and the high protein content of nerve. He suggested that the phosphate was derived from lipid, and that protein and lipid were probably structurally associated. (The *osmazome* listed was a term used to describe a water-soluble tissue extract, containing peptide- and alkaloid-type substances similar to a meat broth or extract.) Considering the dearth of analytical methods and the embryonic concepts of organic chemical components at that time, Vauquelin and his contemporaries had an excellent understanding of cerebral composition which is not too different from modern ideas.

Space does not permit a review of the interesting history of the development of brain chemistry, but the summaries by Thudichum (222, 223), Schmitz (204), Winterstein (249), Page (168), Rossiter (194) and Tower (229) cover the period in detail. The early investigations culminated in the brilliant studies of Thudichum between 1862 and 1901 which are reported in his two books on the chemical constitution of the brain (222, 223). Many of the components of the cerebral lipids which are familiar today were first isolated and identified by Thudichum. His analyses of gray and white matter give good approximations to those of today. Thudichum's work brought an end to an era of uncertainty and confusion about the composition of the brain and ushered in the modern era of investigation on its finer structure, metabolism and mode of functioning which are reviewed in the references cited above.

PRINCIPAL DIVISIONS AND CONSTITUENTS. *Fluid spaces and solutes.* The principal divisions and constituents of the central nervous system are shown in figure 1. The most striking feature is the fact that brain consists mostly of water. Infant brain has an even higher percentage (about 90.5) for both gray and white matter (117). This situation is not unique to brain since it is typical of most organs of the body. There is excellent agreement on the total amount of water in brain, but its compartmentation between extracellular and intracellular spaces is still controversial. The preceding chapters have considered this and related aspects in detail, so that only relevant factors need be covered. Despite objections (9) and proposed modifications (55, 67, 251), it is still

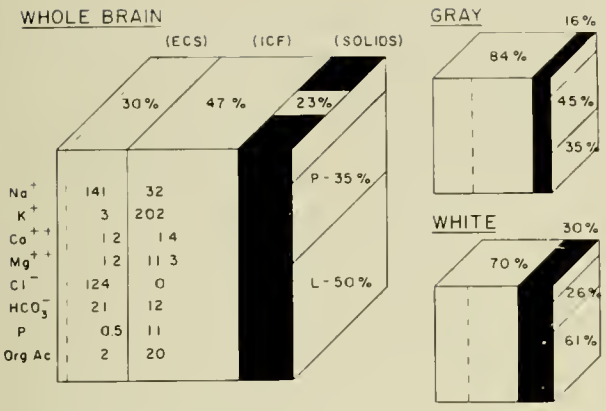



FIG. 1. The gross composition of whole brain and of gray and white matter. Percentages of total solids accounted for as proteins (*P*) and lipids (*L*) are shown at the *right* of each block. For whole brain, the *dotted line* indicates the approximate portions of the extracellular space (*ECS*) occupied by cerebrospinal fluid (on the *left*) and interstitial fluid (on the *right*). The ionic composition of whole brain fluids are expressed in milliatoms per kg of extra- and intracellular $H_2O$, respectively. For gray and white matter, the *dotted line* represents the estimated division of tissue water into extracellular (on the *left*) and intracellular (on the *right*), the former being about 34 per cent for gray and 28 per cent for white. (References: 29, 42, 65, 96, 112, 115–118, 132, 138, 145, 149, 150, 153, 155, 164, 174–176, 182, 212, 221–223, 234, 241, 246, 247, 251, 252.)

TABLE 2. *Components of Cerebral Lipids**

| | Classification† | % Dry Wt. Gray | % Dry Wt. White |
|---|---|---|---|
| | I. Sterols: cholesterol (free) | 5.6 | 14.0 |
| | II. Phosphatides (phospholipids): | (22.3) | (30.7) |
| Cephalins | A. Phosphoglycerides | | |
| | 1. Phosphatidyl choline (lecithin) | 6.3 | 4.6 |
| | 2. Phosphatidyl ethanolamine | 8.1 | 9.4 |
| | 3. Phosphatidyl serine | 3.1 | 7.0 |
| | 4. Plasmalogens (acetal phosphatides) | (0.6)‡ | (1.6)‡ |
| | B. Phosphoinositides | | |
| | 1. Diphosphoinositides | 1.2 | 1.3 |
| | C. Phosphosphingosides | | |
| | 1. Sphingomyelin | 3.0 | 6.8 |
| Sphingolipids | III. Glycolipids | (7.1) | (20.8) |
| | A. Glycosphingosides (cerebrosides) | 5.5 | 16.3 |
| | 1. Sulfatides (cerebron sulfuric acid) | 1.2 | 4.0 |
| | B. Gangliosides | 0.4 | 0.5 |
| | [Strandin]§ | [4.4] | [0.2] |
| | IV. Neutral fat (triglycerides) | 0.3 | |

* References: 21–23, 29, 66, 68, 69, 71, 74–76, 78, 115–118, 128–132, 134, 153, 182.

† After Folch & Sperry (76).

‡ Estimated from McIlwain (153) and Korey (134).

§ Strandin is a high molecular weight complex of ganglioside-type molecules.

generally assumed that the chloride ion is essentially extracellular and may therefore be used as a measure of the extent of the extracellular space.[1] The basis for this assumption has been reviewed by Lowry & Hastings (145). The problems encountered with the myelin sheath (146, 234), with studies on brain slices of a functional extracellular space. The recent electron microscope studies by de Robertis and co-workers (86) and by Luse (147) demonstrate that one type of glial cell, probably the astrocyte (86, 126), behaves as if it is part of the biochemically definable extracellular (chloride) space. In addition, the probability that the lumina of the endoplasmic reticulum of neural cells communicate with the extracellular fluid, either permanently or intermittently (as a type of pinocytosis), is gaining wide acceptance (209). Thus, it appears that the brain conforms to other body tissues in regard to functional divisions of its fluid spaces, but it may utilize somewhat specialized structural features in the discreet organization of these spaces.

[1] For calculation of the chloride space in brain, cerebrospinal fluid $Cl^-$ concentration is taken to represent that of extracellular fluid $Cl^-$ and the space is calculated as follows (149):

$$\text{Extracellular } H_2O \text{ (gm/kg tissue)} = \frac{\text{Total tissue chloride (mEq/kg)}}{\text{Extracellular fluid chloride (mEq/l.)}} \times 100$$

Where extracellular fluid $Cl^-$ concentration is not known, this has been calculated by correction for the Donnan equilibrium effect from serum chloride concentrations (145).

The disagreement between electron microscopists, who have observed little or no space between cells in electron micrographs of brain (248), and biochemists and physiologists, who have maintained that a functional extracellular space must exist to account for observed phenomena, are gradually being resolved. Fixation and embedding procedures employed in the preparation of electron micrograph sections are now recognized to involve shrinkage and often collapse or compression of less well 'suspended' structures. Both the biochemical studies on the distribution of ions in cerebral tissues and the electrochemical data from microelectrode recordings require the presence

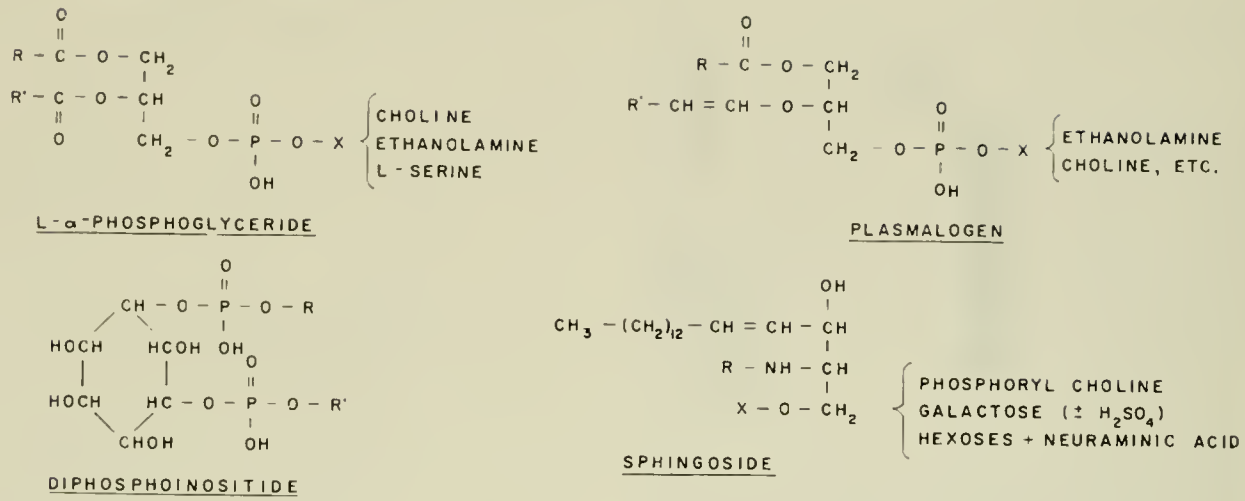



FIG. 2. The basic structural formulas of the constituent compounds of neural lipids. (Cf. table 2.) *R* and *R'* indicate fatty acid chains, esterified with glycerol, inositol or sphingosine. The point of attachment of the nitrogen or carbohydrate compound is indicated by *X*. The sphingolipids (sphingosides) indicated are sphingomyelin, cerebrosides and gangliosides, respectively (13, 38, 71, 183).

*in vitro* (55) and with *in vivo* space measurements (251) have not been resolved and are complicated by tissue swelling *in vitro* and the blood-brain barrier phenomenon *in vivo*. However, the studies of Hiatt (104) *in vivo* and of Thomas & McIlwain (221) *in vitro* on chloride ion depletion by replacement with nitrate clearly indicate that the chloride ion in brain is in complete equilibrium with serum chloride whereas some sodium and the bulk of the potassium in brain are not. Thomas & McIlwain (221) found that only about 2 mEq per kg could be considered as possible intracellular chloride.

With minor reservations it seems safe to assume that the chloride space is equivalent to the extracellular space, or some 30 per cent of the total brain mass, most of which is interstitial rather than cerebrospinal in location. On this basis the concentration of ions per kilogram of extra- or intracellular water can be calculated and such values are given in figure 1. Direct estimations on neurons suggest that their water and solids content approximates that given for intracellular total space (water plus solids) of gray matter in figure 1 (31, 32, 143, 146, 159). Analogous studies on glia have not been reported. If the situation in figure 1 is correct, there is a considerable deficit of intracellular anions compared to the calculated cation concentration (149). This is presumed to be made up by the intracellular proteins and lipids, each accounting for about half the required amount (67, 153). However, a portion of the intracellular potassium is intramitochondrial (110) and, by analogy from other tissues, this may be true for other electrolytes as well (19, 211). There is still much to learn about the distribution of water and electrolytes and their importance in metabolism (92, 221), but it is apparent that neural structures have a role in determining the distribution of certain ions which are involved in neuronal function.

Other solutes beside those just discussed are also present in cerebral water. With the exception of amino acids, most are present in trace or relatively small amounts. Some of them are considered below (table 4).

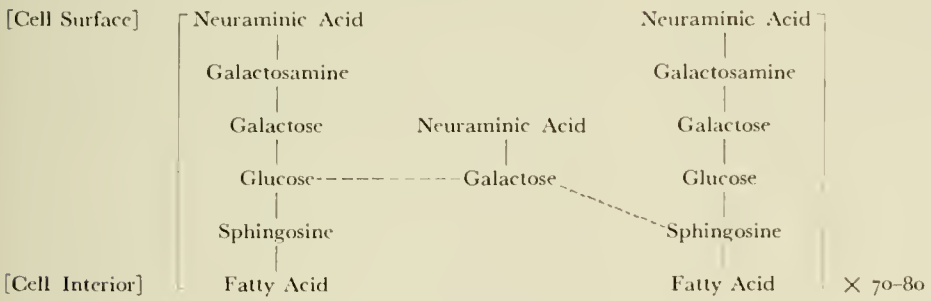
*Solids.* The solids of the brain account for only a small percentage of the total mass, averaging 16 per cent in gray matter and about twice that amount in white (figure 1). The two principal constituents of the solids fraction are proteins and lipids, the residuum accounting for only 15 to 20 per cent of the dry weight. Gray-matter solids predominate in proteins (about half the dry weight), whereas almost two-thirds of white-matter solids are lipids.

LIPIDS. Cerebral lipids are not so much peculiar in type as in concentration; brain, in white matter particularly, is higher in complex lipids than any other organ. Cerebral tissue is further distinguished

by having little, if any, neutral or free fat under normal circumstances. Most of the constituent units of cerebral lipids are found in smaller amounts in one or another of the body's organs. The classification and relative amounts of the components of cerebral lipids are given in table 2, and the basic structures of the various classes are shown in figure 2.

From table 2 the distinction between lipid composition of gray matter and white matter can be readily discerned. Concentrations of cholesterol, sphingomyelin and cerebrosides in white matter are several times those found in gray matter. From the similarity in composition of both cerebral white matter and the peripheral myelin sheath, Johnson *et al.* (115–118) have concluded that these three are typical of myelin and myelinated structures, whereas the phosphatides are more typical of cellular areas. Since there is still some analytical confusion about the cephalin group of phosphatides and about the glycolipids, the individual percentages listed in the table do not entirely correspond to the totals determined independently. This situation is due to the facts that it has only recently been recognized that the cephalin fraction is composed of four related compounds (13, 14, 66, 71, 75, 78, 134, 183), one of which, the plasmalogens, may actually be a group (13, 134, 183), and that the ganglioside structure is still not completely worked out (22, 23, 25, 38, 45, 74, 93, 128–131). As a result there are overlaps in quantities determined by various methods.

The structural formulas in figure 2 represent the basic building blocks of cerebral lipids. How these are formed into macromolecules such as gangliosides and myelin is still poorly understood. Recent studies by Cornforth *et al.* (45) and Bogoch (25) have clarified the structure of gangliosides. Bogoch has proposed the following unit structure for brain ganglioside:




Some 70 to 80 of these units appear to be polymerized together as a macromolecule, arranged along the cell membrane in the orientation indicated. The neuraminic acid is present as the N-acetyl derivative,

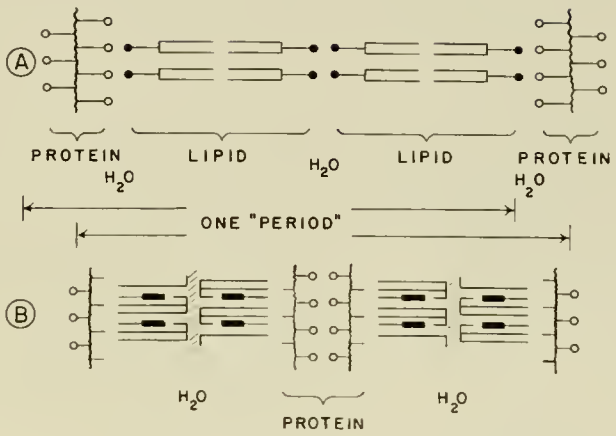



FIG. 3. Proposed models for the macromolecular structure of the myelin sheath. Structure *A* is that suggested by Schmitt (203), and *B* is the modification suggested by Fincan (62). The latter incorporates cholesterol into the scheme, as indicated by the *solid bars*.

the structure of which has been determined by Cornforth *et al.* (45). Studies by Gottschalk (93), Klenk (130) and Bogoch (25) suggest that gangliosides may function as specific receptors (e.g. for viruses) via the neuraminic acid 'surface' groups. From the work of Folch and his collaborators, it is apparent that much of the cerebral lipid is associated with protein as lipoprotein or proteolipid (68, 72, 77) as discussed in the next section. An indication of how such structures may be built up may be inferred from the isolation by Folch & LeBaron (70) of phosphatidopeptides from brain white matter. A different type of complex, called strandin, has been isolated from gray matter (69) and is apparently a macromolecular aggregation of gangliosides or ganglioside-like components (74).

Some idea of the organization of the final structure has been provided by polarized light, x-ray diffraction and electron microscope studies of myelin sheaths (60–64, 134, 172, 197, 201–203). On the basis of

TABLE 3. *A. Components of Cerebral Proteins**

| Type | Characteristics |
|---|---|
| Albumin | |
| Globulin | |
| Collagen and elastin | Restricted to nonneural elements (blood vessels, etc.) |
| Ribonucleoprotein | Mainly in cytoplasm |
| Deoxyribonucleoprotein | Only in nucleus |
| Liponucleoprotein | Lipid content 35% (phosphatides, cerebrosides); accounts for majority of protein-P |
| Phosphoprotein | Similar concentration in gray and white |
| Proteolipids | Type A (mixture): 20% protein; 80% lipid (cerebrosides and phosphatides, ratio 7:1) |
| | Type B: 50% protein; 50% lipid (phosphatides and cerebrosides, ratio 6:4 with half the phosphatide as sphingomyelin) |
| | Type C: 75% protein; 25% lipid (glycerophosphatides) |
| | Concentration of white vs. gray 4:1; a major component of tissue solids; protein moiety trypsin resistant (? = neurokeratin) |
| Neurokeratin | ? same as proteolipid |

*B. Electrophoresis of Water-Soluble Cerebral Proteins*

| % Serum Fractions | Brain Fractions | % Gray | % White | Comment |
|---|---|---|---|---|
| | Fast component | 0.6 | 1.1 | Present in CSF |
| 50 | Albumin | 1.9 | 3.0 | |
| 15 | $\alpha_1$ Globulin | 4.2 | 7.2 | Lipoprotein in serum; glycoprotein in serum |
| | $\alpha_2$ Globulin | 7.8 | 11.7 | Glycoprotein in brain |
| 19 | $\beta$ Globulins | 66.6 | 53.6 | Lipoproteins in serum and brain |
| 11 | $\gamma$ Globulins | 18.9 | 23.4 | |
| 5 | Fibrinogen | | | |

* References: 68, 72, 77, 96, 97, 106, 141, 144, 152.

these observations, diagrams, such as those shown in figure 3, have been proposed. They cannot be taken literally but should be considered to represent a prototype or principle of organization. Finean (62) suggested a modification (figure 3*B*) of Schmitt's (203) earlier conception to account for certain findings in x-ray diffraction patterns and, in doing so, has proposed a role for the cholesterol of the myelin sheath, as illustrated. Basically the structure is visualized as consisting of bimolecular lipid layers oriented radially (to the long axis of the fiber) between concentrically oriented protein chains and incorporating thin water channels. These leaflets or 'periods,' measuring about 170 Å in length, appear to be wrapped around the axon as laminations. This lamellar arrangement can be seen by electron microscopy (60, 61, 172, 197). Finean (64) has reported that, although the basic pattern of myelin is similar for both peripheral and central structures, the latter appears to be only lipid in character, while the former is composed of lipoprotein. Geren (85) has demonstrated that the peripheral myelin sheath is actually produced by and part of the Schwann cell membrane. It is probable, but not yet firmly established, that a similar function for oligodendroglia obtains for central myelinated tracts.

PROTEINS. By comparison with the lipids, information concerning cerebral proteins is scant indeed. Satisfactory methods for protein chemistry are a relatively recent development and the association of many cerebral proteins with lipids has complicated application of these methods. A number of protein components have been isolated from the brain by various methods, but the relative amounts and distribution are in most cases unknown or uncertain. The known components are listed in table 3, together with some of their characteristics. Electrophoresis has recently been applied to cerebral tissues and the results of one such analysis are also given in the table. Comparison of the latter data with analyses on serum protein shows a pattern, which is encountered in most tissues, of low albumen and high globulin percentages, especially for the $\beta$-globulin fractions which contain the main lipoprotein components. The correlation of electrophoretic analyses with the components isolated cannot be established at this time.

Of principal interest for the central nervous system

are the liponucleoproteins, the phosphoproteins and the proteolipids. The first two account for the majority of protein-bound phosphorus in brain (141) and exhibit a high rate of phosphate turnover (24, 47, 98, 215). Proteolipids are complexes which are rather peculiar to brain and occur primarily in the white matter (72). Their general constitution is indicated in table 3. Despite the high protein content, these compounds behave chemically like lipids. Much of the lipid is composed of phosphatides, and the demonstration of phosphatidopeptides in white matter (70) suggests that these may represent intermediate or subunits of some proteolipids. These phosphatidopeptides consist of diphosphoinositide, sphinogosine, or both, plus fatty acids and short peptide chains, averaging seven amino acids in length.

Nucleoproteins, representing aggregations of nucleic acids with proteins, are of great importance to the cell. Essentially all of the desoxyribonucleic acid (DNA) proteins are in the cell nuclei and are concerned with specific nuclear functions such as genetic constitution. Because of this, the amount of DNA per nucleus (or per cell) is constant for all except germinal tissues of a given organism, and this fact has been utilized to permit a simple determination of the total cell population of cerebral tissue samples (99, 191). The DNA content per nucleus of cerebral tissues was found by Heller & Elliott (99) to be 6.5 to 7.1 pgm ($10^{-12}$ gm) for cat, dog and man. The ribonucleic acid (RNA) proteins are present in the nucleolus and especially in cytoplasmic Nissl substance. They are important in protein synthesis and represent the principal sites of amino acid incorporation into peptide and protein structure (82, 89, 113, 121, 140, 184, 208). The mechanisms whereby this is accomplished are not well understood, but it is thought that the protein moiety may provide the enzymes and the nucleic acids a sort of template for the process (11, 48, 184).

The principal units composing the nucleic acids are illustrated in figure 4. The purine and pyrimidine bases are joined to ribose, or deoxyribose, at the point indicated by *X* to form nucleosides which, when phosphorylated, are termed nucleotides. The phosphate addition is usually at the 5′-position on the pentose chain, as shown, but may attach at positions 2′ or 3′ (indicated as *A* and *B* respectively in the figure). DNA differs from RNA in utilizing deoxyribose and containing the pyrimidine thymine instead of uracil; otherwise it is similar to RNA. Nucleotides are aggregated by means of phosphate-

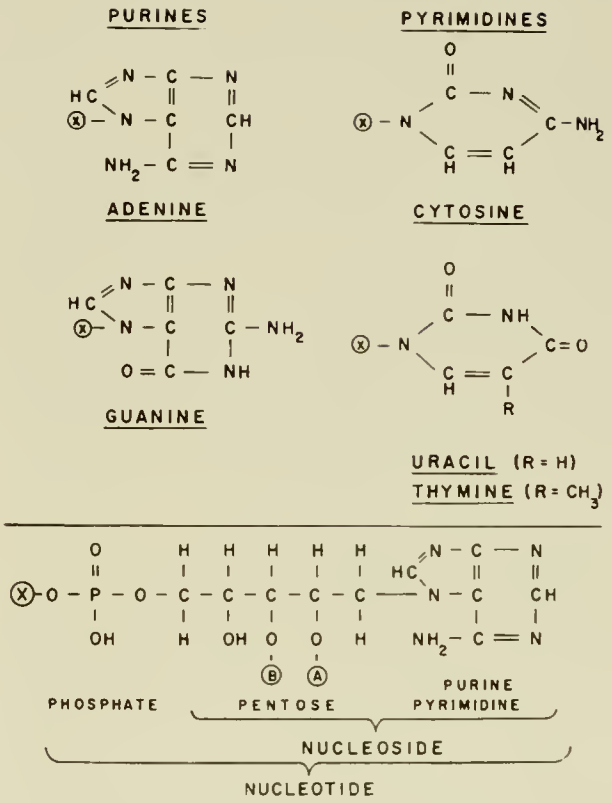



FIG. 4. Structural formulas of the purines and pyrimidines present in nucleotides. The addition of a pentose molecule to these bases at point *X* constitutes a nucleoside, as indicated at the *bottom* for adenine. Addition of a phosphate group to the pentose, usually in the 5′ position, as shown at the *bottom*, constitutes a nucleotide. Additions of further phosphates at *X* (*bottom formula*) result in nucleotide polyphosphates, such as ATP (97).

pentose bridges (at point *A* or *B*) to form nucleic acids. A schematic radical is shown in figure 5. Originally it was thought that nucleic acids were composed of multiples of such tetranucleotide (or pentanucleotide) radicals, but present evidence indicates that the individual nucleotides are 'randomly' distributed through the molecule. An indication of this is found in the analysis of relative proportions of nucleotides isolated from cat brain [see legend to fig. 5 (47)]. Nucleic acid molecules appear to have the form of double-stranded *alpha*-helices with a purine of one strand paired with a pyrimidine of the other by hydrogen bonds (184). The pairing is generally adenine with uracil (or thymine) and cytosine with guanine. Such a structure may be visualized as a spiral staircase in which the purine-pyrimidine pairs represent the stair treads and the

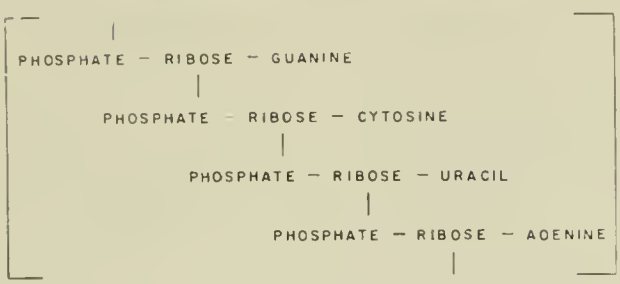



FIG. 5. Schematic representation of a nucleic acid radical. The individual nucleotides are joined by pentose to phosphate bonds at the 2′ or 3′ position on the pentose chain (points *A* and *B*, respectively, of fig. 4, *bottom*). In brain RNA the relative ratios of purines and pyrimidines are A = 1.00; G = 1.47; C = 1.20; U = 0.95 (47). For discussion see text (97).

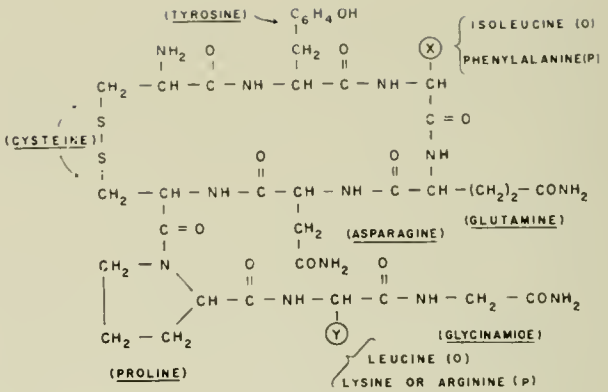



FIG. 6. Structural formulae of the posterior pituitary hormones. The basic formula shown is the same for all hormone varieties, the only differences being in the amino acids substituted at points *X* and *Y* to give oxytocin (*O*) or vasopressin (*P*) of either the lysine or arginine type (18, 49, 50).

ribose (or deoxyribose) phosphate groups 'external' to them form the bannisters.

The nucleotides of figure 4 also have other functions in the cell. By addition of further phosphate groups at position *X*, di- and triphosphonucleotides are formed. Adenosine triphosphate (ATP) is a familiar example derived from adenine, but other purine and pyrimidine bases are proving to have important roles in cellular economy. Uridine polyphosphates (UDP, UTP) are necessary to galactose metabolism (37, 114, 119, 120, 151); cytidine polyphosphates (CDP, CTP) are essential for phosphatide synthesis (122, 196); and guanosine polyphosphates (GDP, GTP) are required for protein synthesis (121) and Krebs' cycle activity at the α-ketoglutarate-succinate stage (199). In addition analogous compounds, di- and triphosphopyridine nucleotides (DPN and TPN, formed from nicotinamide and adenine) and flavine nucleotides (from riboflavin) are important co-enzymes in many steps of energy metabolism. The importance of ATP, DPN, TPN and flavines has been well recognized, but recent studies by Geiger & Yamasaki (84) indicate that the others are equally essential, particularly for the maintenance of structure. The foregoing suggests that nucleic acids, which incorporate most of these nucleotides, might function in the cell, together with enzyme-protein moieties, to carry out reactions demonstrated *in vitro* with the isolated nucleotides. The nucleotides, nucleic acids and nucleoprotein must, therefore, be considered among the more important units of structure, organization and function within the cell (28). The studies on virus nucleic acid-protein relationships by Fraenkel-Conrat (79) illustrate this point nicely. A more general consideration of these subjects has recently been published by Anfinsen (11).

The structures of proteins synthesized by the mechanisms indicated are in general unknown. However, by modern methods of isolation and analysis some of the simpler molecules or units have been identified. Two examples will indicate the sort of structure or organization to be expected.

As a result of the brilliant work of du Vigneaud and his collaborators both determination of the structures and synthesis of the posterior pituitary hormones have been accomplished (18, 49, 50). It is now established that these hormones are elaborated in the supraoptic and paraventricular nuclei of the hypothalamus and are secreted by these neurons down their axons into the posterior pituitary (105, 200). It is probable that the hormones travel with carrier protein [as suggested by Albers & Brightman (8) as well as the renin-angiotensin system (35) in plasma], but the active principles are represented by the structures in figure 6. These are nonapeptides, incorporating nine amino acids by means of peptide bonds (—CH—*NH*—*CO*—CH—). These molecules are not proteins but represent a unit or radical which multiplied ten to thousands of times would constitute a protein.

One of the smaller of such protein molecules is cytochrome *c*, located mainly in mitochondrial cristae of cells (108, 169) and concerned with the end stage in glucose oxidation, the combination of hydrogen, derived from various dehydrogenase systems of glucose degradation, with molecular oxygen to form water. Theorell and his collaborators

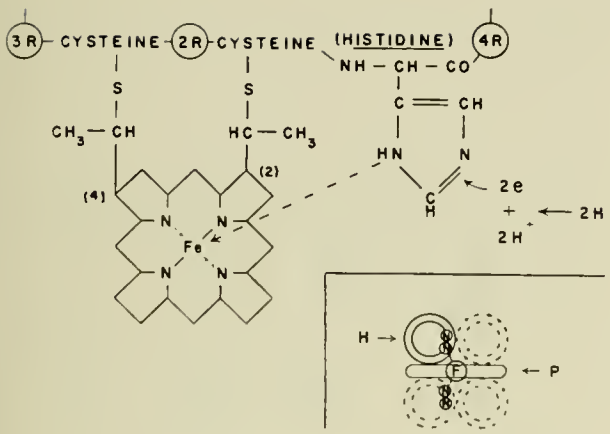



FIG. 7. Structural formula of the hemopeptide of cytochrome C. The porphyrin nucleus is joined to the peptide chain by thioether bonds between cysteine and the vinyl side chains of the 2 and 4 positions on the pyrrole rings. *R* indicates amino acids intervening between those named. The covalent bond between the imidazole ring of histidine and the iron (*Fe*) of the porphyrin nucleus is indicated by the *broken arrow*. The suggested point of electron (*e*) transfer is shown to the *right* of the imidazole ring. *Inset:* Suggested structure of the cytochrome C molecule (axial cross section view). The porphyrin plate (*P*) is visualized as surrounded by helices (*H*) of amino acids. The *solid circle* represents the end-on view of helix formed from the hemopeptide chain with the two nitrogens (*N*) of the histidine imidazole ring and the covalent bond to the porphyrin iron (*F*). Three other peptide helices, as proposed, are also viewed end-on, as indicated by *broken circles*, and one of these is also thought to have a histidine element with similar covalent bonding as indicated (53).

TABLE 4. *Other Components of Brain**

| | Gray | White |
|---|---|---|
| Acid soluble N: % dry wt. | 1.6 | 1.1 |
| (% total N) | (18) | (18) |
| Amino N (% acid sol. N) | (50) | (30) |
| Acid soluble P: % dry wt. | 0.9 | 0.85 |
| Inorganic P (% acid sol. P) | (25) | (25) |
| Ash: % dry wt. | 6.1 | 4.2 |
| Nucleic acids | 1 | |

| Whole Brain (μmole/gm) | | | |
|---|---|---|---|
| Glycogen | 5 | Oxaloacetate | 0.65 |
| Glucose | 4 | DPN (as nicotinamide) | 0.2 |
| Lactic acid | 2.1 | Pyridoxine | 0.06 |
| Pyruvate | 0.2 | Coenzyme A (as pantothenate) | 0.1 |
| Oxygen: | | Riboflavin | 0.01 |
| cerebral 90 | | Cytochrome C (as Fe) | 0.005 |
| vascular 225 | | Ammonia | 0.16 |
| | 315 | Free glutamate, aspartate and deriv | 25 |
| ATP + ADP | 5.0 | Serine | 0.7 |
| Phosphocreatine | 3.0 | Choline (free) | trace |
| Citrate | 0.3 | Ethanolamine (free and phosphate) | 1.0–6.5 |
| α-Ketoglutarate | 1.3 | | |
| Succinate | 0.35 | | |
| Fumarate | 1.2 | | |
| Malate | 0.25 | | |
| Fatty acids | trace | | |

* References: 46, 80, 91, 94, 95, 123–125, 127, 153, 163–166, 185, 213, 214, 218–220.

(53) have elucidated much of the structure of this enzyme-protein, as shown in figure 7. Cytochrome *c* is a metalloprotein containing 0.43 per cent iron in a porphyrin unit which is joined to the protein by thioether bonds. The hemopeptide shown has been isolated and its structure established, although the 12 amino acids vary somewhat from species to species. The functional group is visualized as the imidazole ring of histidine, joined by co-valent bonding to the iron nucleus and accepting the electrons from previous donors to pass them on through mediation of cytochrome oxidase to join with oxygen as water. Ehrenberg & Theorell (53) have determined that the peptide chain exists in the form of an α-helix and visualize the cytochrome-*c* molecule as formed of four such helices enclosing the porphyrin plate, as sketched in the figure. The molecule has a molecular weight of about 12,000, comprising some hundred amino acids and one porphyrin nucleus, with dimensions of the order of 25 × 25 × 40 Å. Such a molecule is, of course, not typical of protein molecules of other types, but it provides an example of how subunits of a protein may be aggregated. The helical configuration has been proposed for other molecules, notably nucleic acids (11, 184), so that this principle of construction may be rather general for proteins and related molecules.

OTHER CONSTITUTENTS. Compared to the three principal constituents of cerebral tissues, water, lipids and proteins, the remaining compounds constitute a small portion of the total (about 4 per cent of the total mass, or 15 per cent of the total solids). Some of these are listed in table 4. Most of the important substrates and metabolites of the brain are present in trace amounts only. Even though the oxygen content appears to be appreciable, this amount at a normal rate of utilization by human brain would last only about 10 sec. (125). Thus, the brain contains no significant store of essential nutrients but depends upon a continual supply from the cerebral circulation. When this supply fails, destruction of cell framework

ensues (1), a situation which rapidly leads to irreversible damage.

By contrast, the brain contains a relatively high concentration of free amino acids, and total amino acids (free and combined) account for about 40 per cent of the total dry weight (153). Some 70 per cent of the amino nitrogen fraction is composed of glutamic and aspartic acids and their derivatives (12, 218–220, 247). This group, in particular glutamic acid (230) and glutamine (231), is present in brain in higher concentrations than in any other organ (219, 241), and is associated with metabolic systems specific to neural tissues (187, 218, 220). Gamma-aminobutyric acid, which is uniquely present in mammals in central nervous system gray matter areas, is of particular interest in this regard (188). These findings have suggested important roles for this group of amino acids in the structural and metabolic economy of the neuron (154, 188, 226–228, 241, 247).

DYNAMIC STATE OF STRUCTURAL COMPONENTS. The original concepts of the chemical structure of brain as a static framework have now been abandoned in the light of better understanding of the blood-brain barrier factor and as the result of studies by isotopic tracer techniques. Turnover of structural components (i.e. metabolic repair, degradation and replacement), which is characteristic of most bodily tissues, is also active among brain proteins, lipids and nucleic acids. With $P^{32}$ as the tracer, rapid turnover of nucleotide phosphorus (47, 215), of phosphatide phosphorus, especially the inositides (6), and of phosphoprotein phosphorus (98) can be demonstrated. Tracer studies with $C^{14}$, $H^3$, $N^{15}$ and $S^{35}$ labeling of compounds show active turnover of lipid and protein constituents (28, 244). Cerebral protein turnover, as judged by incorporation of labeled amino acids, appears to be comparable to turnover of liver proteins (244), whereas most cerebral lipids are probably less active in this respect than lipids in other body tissues (28).

The functional significance of this dynamic state of cerebral constituents remains to be fully explored. The suggested roles for neural lipids of cellular membranes as receptors (25) and in cation transport (73) may be pertinent here. Evidence for the participation of neural proteins in the actions of biologically active amines (40), as sources of endogenous ammonia (40, 232), and in amino group interchanges with free amino acid pools (232) would also appear to be germane. A close association of changes in cytoplasmic nucleic acids with the functional state of neurons has been recognized (87, 113, 157), but what such changes

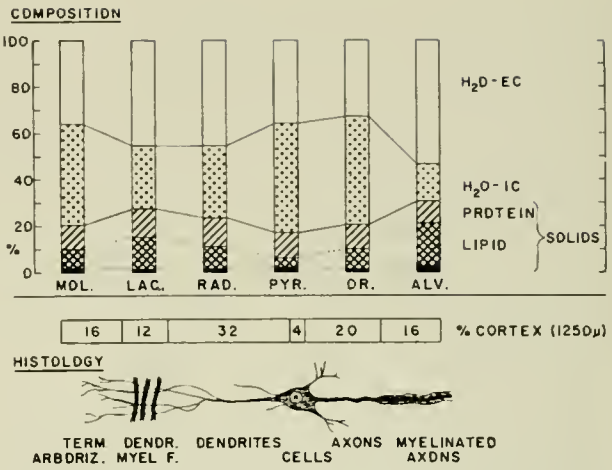



FIG. 8. Chemical composition and histological composition of Ammon's horn (rabbit). The layers (from *left* to *right*) are molecularis (*MOL.*), lacunosum (*LAC.*), radiata (*RAD.*—pure dendrites), pyramidalis (*PYR.*—cell bodies), oriens (*OR.*) and alveus (*ALV.*—myelinated fibers). Data are adapted from Lowry *et al.* (146).

may mean in metabolic terms is still not clear. Although much of the necessary data which would permit an understanding of these phenomena is lacking, it is important to recognize that the majority of cerebral structural components are in a dynamic state and that this fact must certainly have important implications in terms of cerebral function.

### *Microchemical Data*

From the foregoing a general picture of the chemical constitution and structure of the central nervous system and for the most part of its major gray and white subdivisions can be obtained. Because of the lack of uniformity or homogeneity within these divisions, the question arises as to what the pattern of distribution of components is within the subdivisions or layers of various areas and what, if any, are the differences between neurons and glia in these areas. Information regarding white matter is scarce, but the studies of Lowry (143, 146, 216), Robins (189–193) and Pope (177–180), and their respective collaborators, have provided considerable data on various cortical areas and subadjacent white matter.

AMMON'S HORN. Lowry *et al.* (146) chose to study, with the aid of microchemical methods, the constitution of Ammon's horn, a cortical area in which the various elements comprising cortical gray matter

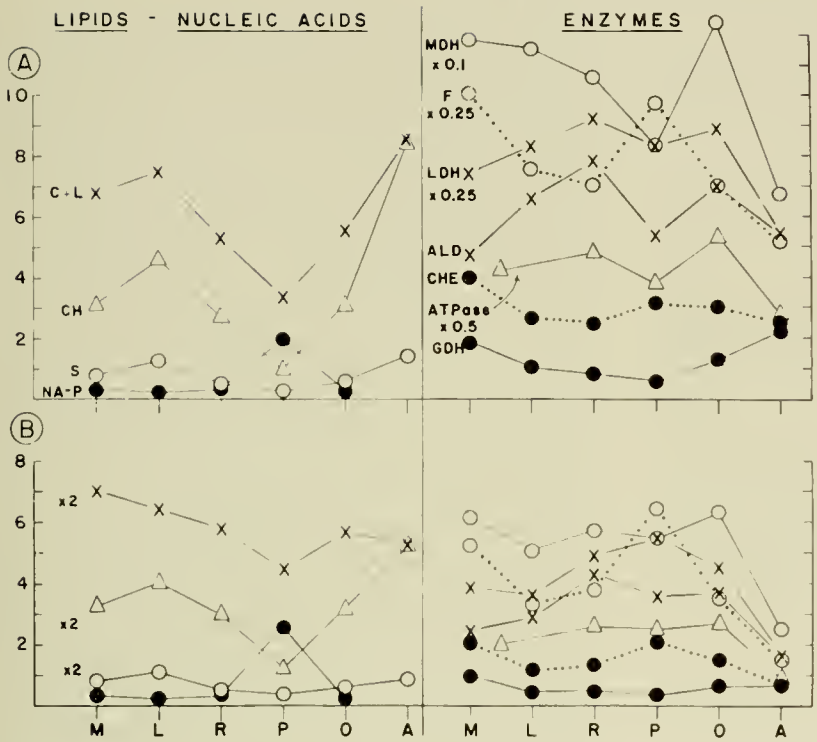



FIG. 9. Variations of lipid components, nucleic acids and seven enzymes in layers of Ammon's horn (rabbit). The plots in *A* are per kg of protein and in *B* per kg dry weight. Units for cephalins plus lecithins (*C* + *L*), cholesterol (*CH*), sphingomyelin (*S*) and nucleic acid phosphorus (*NA-P*) are moles per appropriate unit weight. Units for enzymes are moles per hr. per unit weight. Enzymes are (reading from the *top*) malic dehydrogenase (*MDH*), fumarase (*F*), lactic dehydrogenase (*LDH*), aldolase (*ALD*), cholinesterase (*CHE*), adenosinetriphosphatase ($Mg^{++}$ activated) (*ATPase*) and glutamic dehydrogenase (*GDH*). In order to achieve convenient plots, actual values in many cases have been multiplied by some factor as indicated. For enzymes in plot *B* the factors are the same as in plot *A*; for lipids no factor was necessary in *A* but, as indicated in *B*, the actual values are × 2. Data are taken from Lowry *et al.* (146) and Strominger & Lowry (216).

are quite distinct one from another. By serial sectioning, layers composed essentially of dendrites, of cell bodies or of myelinated axons could be obtained for analysis. The results of this study are summarized in figures 8 and 9. In general composition, cell bodies are limited to 4 per cent of the total cortical volume while the dendrites are found in over half the total. Fluid spaces are of the same order in all layers, except the myelinated layer, while solids are lowest in the cell body layer and highest in the two layers containing myelinated fibers, due to the increased lipid component. It is noteworthy that protein content is relatively constant throughout all layers.

The layer distribution of several solid components and representative enzymes are shown in figure 9, plotted both in terms of unit weight of protein and unit dry weight. [Complete data may be obtained by reference to the original reports (143, 146, 216)]. The plots per unit weight of protein also reflect the trends for a plot per unit wet weight (not shown), as inspection of figure 8 would indicate. Correlation of lipids and nucleic acids with the histological picture are good, the former being high in myelinated layers and low in the cell body layer, the latter showing a peak only in the cell body layer. Cholesterol would appear to be a good indictor of relative degree of myelination per layer (cf. table 2). Enzyme activities are relatively low in the cell body layer and high in dendritic layers, although this is less apparent when related to dry weight rather than protein. These results, together with the relatively larger volume of dendrites compared to cell bodies, have led Lowry *et al.* (146) to reaffirm Holmes' (111) view that neural gray matter metabolism is largely dendrite metabolism.

OTHER CORTICAL AREAS. From such a general picture, the more complex cortical areas can be more easily understood. Similar studies of motor and visual cerebral cortex and cerebellar cortex (excluding the Purkinje cell layer) have now been reported by Robins and collaborators (189–193), and analogous studies on somatosensory and frontal cerebral cortex for enzyme activity have been carried out by Pope and his group (177–180). Some representative data for motor and visual cortex are shown in figures 10 and 11. Complete data may be obtained in the original reports (191–193).

As indicated earlier, total cell densities for the respective areas are relatively constant layer by layer, including the white matter, although the visual cortex contains an average twice that of the motor cortex. Both dry weight and cholesterol increase in the deepest layers, especially for the

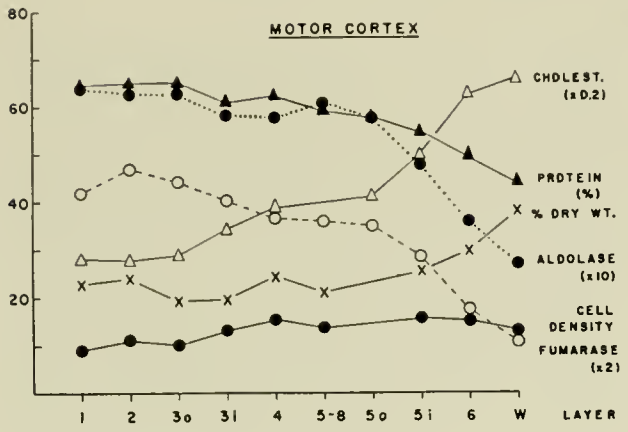



FIG. 10. Layer by layer plot of various constituents of motor (agranular) cortex from the monkey. Cholesterol is expressed in mmole per kg dry weight; aldolase and fumarase are expressed in mole per hr. per kg dry weight—all by the factors indicated. Cell density is expressed as $10^4$ cells per cu mm. [Adapted from Robins *et al.* (191–193).]

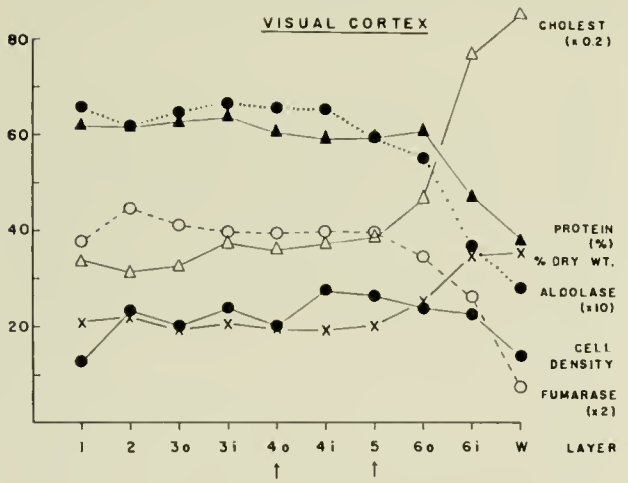



FIG. 11. Plot, identical to that of fig. 10, for visual (striate) cortex from the monkey. The *arrows* at layers *4o* and *5* indicate the position of the outer and inner lines of Baillarger, respectively. Note the lack of significant change in cholesterol content of these two layers. [Adapted from Robins *et al.* (191–193).]

subadjacent white matter, as an indication of increasing myelination. These changes are mirrored by decreases in protein and enzyme activities in the same regions. Actually, until the deepest layers are reached, most components are surprisingly constant from layer to layer, even on subdivision of each layer (192), although Pope (177) found a somewhat more irregular distribution for certain enzymes. It is also of interest that the levels of components and enzyme activities are of the same order in various cortical areas studied, although they differ not only in cellular density but in histological and functional characteristics. This situation is also apparent for other components such as the acetylcholine system (225, 233), glutamic acid and glutamine (230, 231), and sodium and potassium (unpublished observations).

In such studies, estimation of enzyme activities are done with a view to ascertaining distribution in relation to histological organization. While such correlations may in general be correct, most tissues provide an excess of enzymes, so that under normal conditions their concentration is rarely, if ever, the limiting factor in rates of reactions. This fact is illustrated nicely by several examples derived from deficiency and toxicity studies (44, 161, 162, 228). When acetylcholinesterase is irreversibly inactivated by alkylfluorophosphates, clinical signs of toxicity do not appear until enzyme inactivation has reached 90 per cent or more (161). A generous supply of enzymes is provided in part at least because renewal of depleted enzyme requires time. In the example cited, the rate of regeneration was 4 per cent per day during the initial two weeks and 0.4 per cent per day thereafter, so that some 140 days were needed to achieve control levels of activity (161).

While most of the constituents of the central nervous system are fairly consistent in amount from species to species, there are certain cortical constituents and activities which depart from this rule. These are represented by activity of the acetylcholine system (233) and oxygen uptake or respiration and possibly anaerobic glycolysis (54, 56). The first two decrease in going from small to large species of animals, acetylcholine activity correlating with increasing brain weight (233) and oxygen uptake correlating with increasing body weight (56) of the respective species. Anaerobic glycolysis shows an increase with increasing size of species, but its correlation with body or brain weight has not been assessed. The significance of these latter two observations in terms of functional organization is not at present apparent. The decrease in acetylcholine activity appears to parallel the decrease in cortical neuron density which is also correlated with increasing species brain weight (207, 225, 233). Some of the possible implications of this parallelism are discussed elsewhere (225).

In addition to the foregoing, there are differences of distribution for certain constituents among various areas of gray matter in a given species. This is true

for components of the acetylcholine system (36, 59, 148, 225), for other neurohumors and related compounds (10, 167, 187, 240), and to a lesser extent for oxygen uptake and glycolysis (54). The meaning of these differences from a structural standpoint and a more complete definition of differences among various gray matter areas remain to be elucidated. The application of the microchemical techniques discussed above to such areas as the thalamus, caudate nucleus and hypothalamus, for example, would be most interesting.

NEURONS VS. GLIA. The evidence reviewed so far has not indicated what proportions of components and enzyme activities can be ascribed to neurons or to glia, or what differences may occur between them. The fact that enzyme activities drop rather abruptly in white matter beneath the cortex while total cell density does not decrease in parallel (fig. 8, 9), together with the fact that the glial populations in cortical gray and subcortical white are roughly comparable (table 1), would suggest that the metabolic activity of glial cells is substantially less than that of the neurons, particularly since the neurons make up only about 20 per cent of the cortical population. Whether glial and neuronal compositions are different cannot be deduced from such data, and there have been no studies on glia comparable to those for neurons to be discussed in the next section. By electron microscopy, glia and neurons appear to contain the same cellular elements and differ only in relative amounts visible (172).

Substantiation of lesser metabolic activity for glia has been provided by several studies (3, 100, 135). Results of the study by Heller & Elliott (100) have been summarized in table 5. Per unit weight, cortical tissue respires and glycolyzes more rapidly than white matter (from the corpus callosum); but when the data are calculated in terms of cell numbers, the cerebral cortex exhibits the highest activity, cerebellar cortex the lowest, and corpus callosum intermediate between the two. These results suggest that glial cells may respire more rapidly than some neurons, but in cerebral cortex neurons would appear to respire more rapidly than either cerebellar neurons or glia, possibly due to their larger size and more extensive processes. Korey & Orchen (135) have recently confirmed some of these findings by the use of a somewhat more detailed method of tissue fractionation. On the basis of these data, it is estimated that for both cat and man about 75 per cent of the respiration (oxygen consumption) of the cerebral cortex is attributable to neurons, although they comprise only about 20 per cent of the total cortical cell population. Korey & Orchen (135) have calculated that gray matter accounts for 73 per cent of total brain respiration and that neurons (including axoplasm) utilize some 65 per cent of the total oxygen consumed by the brain. These investigators also point out that if the respiratory rate of neurons is compared with that of hepatic parenchymal cells under the same experimental conditions, the neuronal rate is four times higher on a per cell basis. It is probable that it would be more correct from a functional standpoint to refer oxygen consumption to some parameter of cell size (volume, surface area) rather than to cell number or tissue weight (135). A preliminary estimate for cat cerebral cortex, in terms of unit volumes of neurons and of glia, suggests that the respiratory rate of cortical glia in such terms is only one half that of the neurons and that the 'extra' neuronal oxygen consumption may in part be attributable to special metabolic systems unique to neurons (232).

If the data on tumors can be applied to normal tissues it would appear that the oligodendroglia

TABLE 5. *Respiration and Gylcolysis of Various Brain Areas**

| Tissue | Total Nuclei per $mm^3 \times 10^2$ | $O_2$ Uptake (μl/hr.) | | Anaerobic Glycolysis (μl/hr.) | |
|---|---|---|---|---|---|
| | | per mg fresh wt. | per $10^6$ nuclei | per mg fresh wt. | per $10^6$ nuclei |
| *Cat* | | | | | |
| Cerebral cortex | 128 | 2.4 | 19. | 1.35 | 10.5 |
| Corpus callosum | 135 | 0.77 | 5.7 | 0.38 | 2.8 |
| Cerebellar cortex | 808 | 2.1 | 2.6 | | |
| *Dog* | | | | | |
| Cerebral cortex | 148 | 2.15 | 14.5 | | |
| Corpus callosum | 145 | 0.69 | 4.8 | | |
| Cerebellar cortex | 568 | 1.7 | 3.0 | | |
| *Man* | | | | | |
| Cerebral cortex | 131 | 1.9 | 14.5† | 2.0 | 15.5† |
| Corpus callosum | 112 | | | 0.33 | 3.05 |
| Temporal lobe white | | 0.75 | 6.7† | | |
| Cerebellar white | 42 | 0.33 | 7.9 | | |
| Medulloblastoma‡ | 1170 | 0.52 | 0.44 | 0.34 | 0.29 |
| Astrocytoma‡ | 210 | 0.19 | 0.91 | 0.18 | 0.86 |
| Oligodendroglioma‡ | 298 | 1.4 | 4.7 | 0.63 | 2.1 |

* From data of Heller & Elliott (100).

† Assuming nuclear counts made on other areas apply.

‡ $O_2$ uptake in bicarbonate-buffered medium. All others in phosphate-buffered medium. With normal tissues, values in bicarbonate about 70% of those in phosphate.

respire much more rapidly than astrocytes (or other nonneuronal elements). Other studies lend support to this suggestion (3, 237). Since oligodendroglia are relatively more numerous in white matter (table 1), they may account for the bulk of the nonneuronal element respiratory activity. There are other clear differentiations between cortical neurons and glia. Using differential histochemical techniques, Koelle (133) has found that acetylcholinesterase is restricted largely to neuronal elements, whereas the serum type ('non-specific' or 'pseudo' cholinesterase) resides in the glial cells and blood vessels. Studies of the distribution of enzymes responsible for the synthesis and for the further metabolism of γ-aminobutyric acid demonstrate that they are restricted to gray matter areas of the central nervous system (7, 142, 198). The distribution of γ-aminobutyric acid content in various parts of the brain conforms to that for the enzymes and indicates that the γ-aminobutyric acid system is probably exclusively a neuronal system (230, 231). Further comparative studies along these lines should be most informative.

## ORGANIZATION OF THE NEURON

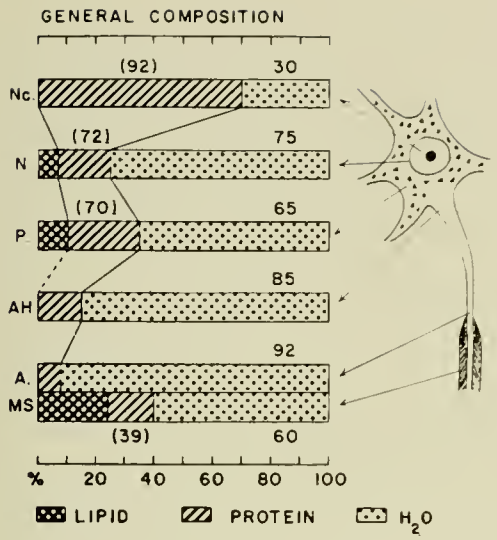
### *General Composition*

The developments of cytochemical and cytological methods, using ultraviolet and x-ray microspectrographic analysis, microdissection with microchemical analyses, cell fractionation by high-speed centrifugation, and electron microscopy, have made it possible to determine something of the composition, structure and organization of the neuron.[2] The principal advantages and disadvantages of these methods in their application to neural tissues have been discussed and summarized by Robins & Smith (190, pp. 315–321). Data from a number of sources have provided a fairly good idea of the general composition of certain representative neurons (30–32, 51, 52, 57, 58, 87, 113, 143, 157, 159). A summary for the anterior horn cell of spinal cord derived from these sources is shown on the left in figure 12.

With the exception of the nucleolus, all areas of the neuron consist primarily of water, and there is a fairly regular, progressive increase in its percentage from nucleolus to axoplasm. Similar findings for nuclear and cytoplasmic areas of spinal ganglion cells, supraoptic nucleus neurons and Purkinje cells have been reported (31, 32, 159); but neurons from Deiter's nucleus apparently contain a greater proportion of solids (31, 32). The general picture, shown in figure 12, appears to apply to all species studied (rabbit, cat and rat) and does not differ significantly from that for liver cells (159). Most of the nuclear and perikaryal solids are protein in nature, but each area contains about 30 per cent lipids. The nucleolus does not seem to contain any lipid and the axoplasm contains a relatively small amount (percentage not known). The composition of the myelin sheath of the axon is essentially similar to that inferred from studies of Ammon's horn (fig. 8), except for a somewhat greater water content. By comparing the data in figure 12 with those given in figures 1, 8, 10 and 11, it is apparent that the general constitution of cortical gray matter is very similar to that of the neuron. It is probable that the glial cells would, on this basis, have a similar composition, although that remains to be determined.

The nucleolus stands out as a very different structure. Its high percentage of solids confers upon it a much higher density than any other cellular element. Under the effects of gravity, nucleoli of cells will fall through the nuclear fluid and, under centrifugal force, nucleoli have been observed to pass out through both nuclear and cell membranes (238). Nucleolar solids appear to be almost entirely protein with a small percentage of associated ribonucleic acids. Vincent (238) has concluded that the nucleoli of cells must be solid or nearly solid bodies containing proteins in a state of considerable dehydration. Hydén (113) has pointed out that the large nucleolus of neurons, together with the large amounts of perikaryal ribonucleoprotein (Nissl bodies), are features characteristic either of growing cells or those in which intense production of protein occurs. He has suggested, on the basis of ultraviolet microspectrographic studies, that during axonal regeneration (after experimental section), there is nucleolar production of ribonucleic acids and protein which migrate to the exterior of the nuclear membrane

[2] Staining or 'slide' histochemistry has been largely omitted from this consideration because of the lack of quantitation inherent in current methods, of difficulties in localization due to diffusion and nonspecific adsorption, of artefacts introduced by embedding and fixation of tissues, and of the lack of methods for a number of important constituents. This is not to imply that the other methods have no analogous disadvantages nor to detract from the many valuable studies employing these techniques which have provided information on the presence and distribution of enzymes and other constituents, such as the cholinesterases (81, 133, 224) and neurosecretory activity of hypothalamic neurons (200). For further discussion and references the paper by Robins & Smith (190) should be consulted




| FRACTIONAL COMPOSITION | |
|---|---|
| CYTOLOGICAL | CYTOCHEMICAL |
| A. NUCLEUS | I. NUCLEI |
| 1. NUCLEOLUS | NUCLEOLI |
| 2. ASSOC. CHROMATIN | NUCLEOPLASM |
| NUCLEOLAR CAPS | DEBRIS (CELL MEMBRANES, MYELIN SHEATH) |
| CHROMOCENTER | |
| SATTELLITE (SEX) | |
| 3. NUCLEOPLASM | |
| B PERIKARYON | |
| 1. NISSL BODIES | II MICROSOMES |
| ENDOPLASM. RETIC. GRANULES | PARTICULATE |
| | SUPERNATANT |
| 2. MITOCHONDRIA | III. MITOCHONDRIA |
| CRISTAE | PARTICULATE |
| MATRIX | SUPERNATANT |
| 3. AGRAN. RETICULUM | IV. SUPERNATANT |
| 4. FIBRILLAR NET | LIPID |
| 5. LIPID, PIGMENT | AQUEOUS |

FIG. 12. The general and fractional cytological and cytochemical composition of the neuron. Percentages of water in the various cell fractions are per unit mass of the respective fraction. The values of protein for each fraction (given in *parentheses*) are as percentages of the total solids per unit mass of the respective fraction. See text for discussion. (References: 15–17, 30–32, 51, 52, 57, 58, 61, 108, 109, 113, 143, 157, 159, 160, 169–173, 205, 206, 235, 243.)

to mediate there the formation of perikaryal protein (113). There is both support (89) and contrary evidence (87, 121) regarding this concept.

*Fractional Composition*

From a cytological standpoint the nucleus and perikaryal cytoplasm are composed of a number of different elements which have been recently confirmed by electron microscopy together with delineation of their finer structure (61, 170, 172, 173, 243). These are summarized in figure 12, based on the descriptions of Hydén (113) and Palay (172, 173). With the introduction of centrifugal fractionation of cell constituents by Bensley & Hoerr (20) and its amplification by Claude (41), the biochemist has been provided with a means of studying some of the same cellular elements in isolation. Fractions obtained in this way are also summarized in figure 12. Such studies have been carried out primarily on liver cells and have provided a wealth of data (109, 205, 206). Unlike the liver, which is relatively homogeneous, the central nervous system does not lend itself so well to this type of study since the fractions obtained include elements from all cell types present.

Several such studies have been carried out, providing a general idea of the chemical organization of cell components, which probably applies in general to the neuron (2–5, 28, 33, 34, 39, 48a, 83, 90, 102, 110, 156, 186, 195, 235, 243). A composite summary of these results is presented in table 6. Since the data are composites, they may not represent absolute values for the various fractions; but the general relationships indicated are probably representative of the actual situation.

There are some significant but not unexpected differences in composition. Virtually all the DNA is in the nuclear fraction, whereas the RNA is primarily associated with the microsomal fraction (equivalent to the Nissl bodies). By electron microscopy the Nissl bodies have been shown to be composed of a vesicular membrane (endoplasmic reticulum) surrounded by clusters of small granules about 10 to 30 mμ in diameter (173). When these two components are separated by ultracentrifugation, at least 80 per cent of the RNA content is found with the granules (2, 171, 224), suggesting that they are essentially pure ribonucleic acid and ribonucleoprotein. It is of interest that this same microsomal fraction contains the bulk of cellular phosphatides which, in contrast to the RNA, appear to be primarily associated with the membraneous element.[3]

[3] Mitochondria from liver have been similarly fractionated into the particulate matter (cristae) and fluid matrix (108). The cristae appear to carry the oxidative enzymes bound to the membranes, while the matrix contains soluble enzymes such as dehydrogenases, potassium and other solutes (108, 160, 169). Lehninger *et al.* (137) have succeeded in chemically

TABLE 6. *Cell Fractions**

| Fraction | Composition as % of Total | | | | | Enzyme Distribution as % of Total (Estimated) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total N | Nucleic Acid P | | Phosphatide P | $K^+$ | Glycolytic enzymes | Oxidative enzymes | Protein synthesis† | Lipid synthesis‡ |
| | | RNA | DNA | | | | | | |
| Nuclei | 8 | 12 | 100 | 17§ | 17 | 10 | 10 | 15 | (0) |
| Mitochondria | 21 | 15 | 0 | 20 | 28 | 15 | 75 | 15 | ++ |
| Microsomes | 38 | 50 | 0 | 60§ | | 0 | 10 | 60 | + |
| Granules | | 40 | | 18 | 53 | | | | |
| Residual particulate | | 10 | | 42 | | | | | |
| Supernatant | 33 | 23 | 0 | 2 | | 75 | 5 | 10 | (+) |

* References: 2–5, 27, 28, 33, 34, 39, 48*a*, 83, 90, 102, 110, 156, 171, 181, 186, 195, 208, 210, 235, 243.

† Estimated from specific activities of proteins during incorporation of radioactive amino acids.

‡ No quantitative data; relative distribution indicated by + signs.

§ Lipid % dry wt. of fraction for nuclei 27; for microsomes 57.

It is probable that the values for phosphatides reflect the distribution of total lipids since the phosphatides make up the bulk of cellular lipids, with the possible exception of the supernatant fraction. In liver the lipid of this fraction is mostly neutral fat (210), and in brain preparations this fraction tended to separate into lipid and nonlipid portions (3). It is also probable that the values for total nitrogen reflect protein distribution, although no direct data are available. One other point of interest is the high concentration of potassium in mitochondria. It has been suggested that this may account for the nondiffusible fraction of potassium in brain tissue encountered by a number of investigators (110). When these results on neural tissue fractions are compared with those for liver, there is in general a close correspondence (19, 109, 136, 171, 181, 205, 206, 210, 211, 217).

The distribution of enzyme systems, summarized in table 6, also resembles that for liver cell fractions. The glycolytic system (converting glucose to lactic acid) resides principally in the supernatant fraction, although it requires ATP generated by mitochondria for its full activity (3, 48a, 83, 102, 139, 156). In contrast to liver, brain mitochondria possess considerable glycolytic activity of their own in addition to that in the supernatant (3, 39, 48a, 83, 102, 156). However, the mitochondria are preeminent in being the principal site of oxidative enzymes (concerned with the complete oxidation of glucose and its associated generation of ATP) (2–4, 33, 34, 39, 48a, 83, 102). Brain mitochondria differ in another respect from liver mitochondria in possessing all links in the oxidative chain (34, 83). Brain mitochondria also appear to be the site of production and metabolic utilization of γ-aminobutyric acid, as well as a major site for its storage (154, 230, 231; unpublished observations). It is possible that brain cells also differ from liver cells in their site of DPN production, which in liver is a nuclear function (109), since added DPN has been reported unnecessary for brain mitochondria (33). This point is not yet clear, however.

Lipid synthesis by neural cell fractions appears to conform to that found in liver cell fractions (27). Mitochondria and microsomes are the primary sites of such activity, supplemented to varying degrees by requisite contributions from the supernatant fraction (6, 28, 37, 196). Because of the complexity of neural lipids, requiring carbohydrate and amino acid components as well as the more usual lipid units, it is understandable that lipid synthesis should involve several fractions and be dependent upon the particular type of lipid being synthesized. The brain also conforms to liver in respect to protein synthesis. In liver, the microsomal fraction is primarily responsible for incorporating amino acids into proteins, supplemented by supplies of cofactors (such as ATP) from mitochondria and supernatant fractions (121, 140, 208). Microspectrographic analyses of neurons suggested that they utilized these same principles

disrupting mitochondria and find that the enzyme assembly necessary for complete substrate oxidation is retained intact and firmly bound to relatively small fragments of the mitochondrial structure (cristae).

(1, 87, 113, 157), and recent studies by Waelsch and co-workers have provided direct confirmation by demonstrating very active incorporation of amino acids into proteins by brain microsomes (43, 82, 245). These findings have been nicely complemented by the histochemical demonstration of the presence of and synthesis of a protein enzyme, acetylcholinesterase, in the endoplasmic reticulum (microsomal fraction, Nissl substance) of neurons (81, 224).

This brief survey has been intended to indicate the principal features of cellular organization, since the details of metabolism are covered in succeeding chapters. It is apparent that the various cell elements are not completely independent entities from a functional standpoint. As Hogeboom *et al.* (109) put it, the cell is not simply a haphazard bag of enzymes nor is it biochemically just a nucleus or collection of mitochondria, but it is a complicated mosaic of structural units endowed with specific chemical properties and, although some functional autonomy is suggested, in no instance does this appear to be complete since the structural units appear to be mutually dependant on one another for their contributions to the metabolism of the cell.

These views have been amply substantiated by the growing recognition of factors which are important in the regulation of cellular metabolism (250). Two of these factors are pertinent to this discussion. Brady (26) has pointed out that the synthesis of fatty acids, cholesterol and sphingosine require, as cofactor, reduced triphosphopyridine nucleotide (TPNH) and that the principal source of TPNH is from the oxidation of glucose via the hexose monophosphate (HMP) shunt pathway. In contrast to neonatal brain where synthesis of these lipid components is active, adult brain exhibits relatively little turnover of these constituents. The metabolic pathways originally devoted primarily to active synthesis are in the mature nervous system shifted to sustaining reactions, and there is little metabolism via the HMP shunt pathway and hence little TPNH available. Yet the enzymes of the HMP shunt pathway are still readily demonstrable in adult brain tissue, expecially in myelinated areas. Brady (26) concludes that it is not the lack of enzymes which has caused this shift in metabolic emphasis but some other regulatory mechanism such as suppression of these synthetic pathways by accumulation of biosynthetic end products.

A second and possibly not unrelated factor is that of compartmentation. Some 50 years ago Hofmeister (107) suggested that the enzymes necessary for the synthesis and for the breakdown (utilization) of glycogen must be separated within the cell or net storage of glycogen would be unlikely to occur. With the advent of isotopic tracer techniques for studying cellular metabolism, evidence for compartmentation phenomena has become increasingly common (250). There are now at least three examples of cellular metabolic compartmentation in the central nervous system: phosphorylation of hexoses (239), synthesis of glutamine (245) and synthesis of $\gamma$-aminobutyric acid (McKhann, Albers & Tower, unpublished observations). Undoubtedly there will be many more. Anatomists and physiologists have dealt with compartmentation at tissue and cell levels for many years; now the biochemist must also deal with it in intracellular terms. It is obvious that the segregation of substrates, cofactors and enzymes within the cell imposes regulatory actions upon processes in one compartment which depend upon metabolic activity in another. In addition the interaction of processes in various compartments poses problems in terms of transport among them and proper distribution of necessary substrates, cofactors and products. Compartmentation is of great importance at the metabolic level but it also must have fundamental significance for the functional activity of the cell as a whole. A recent review by Waelsch (245) considers these points as they may apply to the central nervous system.

From the foregoing data some idea of the kind of cellular organization to be expected in cells of the central nervous system, both in terms of structure and function, can be obtained. It is difficult to evaluate how representative the data are for neurons. The analyses of fractions of gray and of white matter by Abood *et al.* (3) and by Korey & Orchen (135) are the only ones reported, and their results are similar to those of Heller & Elliott (100) in that enzyme activities of white matter fractions are much less than those of gray. However, the pattern of distribution among the fractions is essentially similar in both types of tissue. It seems likely that the neuron will prove to have a cellular, chemical organization which resembles essentially that outlined in table 6. As Hogeboom *et al.* (109) and Waelsch (245) suggest, these data would seem to bear on that aspect of differentiation involving strategic intracellular location of the several specifically endowed elements, so that their individual activities could be efficiently integrated in the overall function of the cell and tissue. It is pertinent to recall that, by electron

microscopy, mitochondria are particularly prominent in neuronal dendrites and are also found along the extent of the axoplasm (172, 173), whereas Nissl bodies are characteristic of perikaryal cytoplasm.

Clearly, the present state of knowledge does not permit a synthesis of the facts and suggestions into a complete chemical architectural fabric, but this no longer seems to be an unattainable reality. The implications of what is known or reasonably certain must have important bearings on the physiology of the normally functioning nervous system and in numerous types of disordered activity.

## REFERENCES


1. Abood, L. G. and A. Geiger. *Am. J. Physiol.* 182: 557, 1955.
2. Abood, L. G. and R. W. Gerard. *J. Cell. & Comp. Physiol.* 43: 379, 1954.
3. Abood, L. G., R. W. Gerard, J. Banks and R. D. Tschirgi. *Am. J. Physiol.* 168: 728, 1952.
4. Abood, L. G., R. W. Gerard and S. Ochs. *Am. J. Physiol.* 171: 134, 1952.
5. Abood, L. G. and L. Romancheck. *Exper. Cell. Res.* 8: 459, 1955.
6. Agranoff, B. W. In: *Neurochemistry of Nucleotides and Amino Acids*, edited by R. O. Brady and D. B. Tower. New York: Wiley, 1960, p. 38.
7. Albers, R. W. and R. O. Brady. *J. Biol. Chem.* 234: 926, 1959.
8. Albers, R. W. and M. K. Brightman. *J. Neurochem.* 3: 269, 1959.
9. Allen, J. N. *A.M.A. Arch. Neurol. & Psychiat.* 73: 241, 1955.
10. Amin, A. H., T. B. B. Crawford and J. H. Gaddum. *J. Physiol.* 126: 596, 1954.
11. Anfinsen, C. *The Molecular Basis of Evolution.* New York: Wiley, 1959.
12. Ansell, G. B. and D. Richter. *Biochem. J.* 57: 70, 1954.
13. Baer, E. *Canad. J. Biochem. & Physiol.* 34: 288, 1956.
14. Baer, E. and J. Maurukus. *J. Biol. Chem.* 212: 25, 1955.
15. Barr, M. L. *Exper. Cell Res.* 2: 288, 1951.
16. Barr, M. L. and E. G. Bertram. *Nature, London* 163: 676, 1949.
17. Barr, M. L., E. G. Bertram and H. A. Lindsay. *Anat. Rec.* 107: 283, 1950.
18. Bartlett, M. F., A. Jöhl, R. Roeske, R. J. Stedman, F. H. C. Steward, D. N. Ward and V. du Vigneaud. *J. Am. Chem. Soc.* 78: 2905, 1956.
19. Bartley, W. and R. E. Davies. *Biochem. J.* 52: xx, 1952.
20. Bensley, R. R. and N. Hoerr. *Anat. Rec.* 60: 449, 1934.
21. Blix, G. *Ztschr. physiol. Chem.* 219: 82, 1933.
22. Blix, G., E. Lindberg, L. Odin and I. Werner. *Nature, London* 175: 340, 1955.
23. Blix, G., L. Svennerholm and I. Werner. *Acta Chem. Scand.* 6: 358, 1952.
24. Bodian, D. and D. Dziewiatkowski. *J. Cell. & Comp. Physiol.* 35: 155, 1950.
25. Bogoch, S. *Neurology.* In press.
26. Brady, R. O. In: *Neurochemistry of Nucleotides and Amino Acids*, edited by R. O. Brady and D. B. Tower. New York: Wiley, 1960, p. 113.
27. Brady, R. O. and S. Gurin. *J. Biol. Chem.* 199: 421, 1952.
28. Brady, R. O. and D. B. Tower (editors). *Neurochemistry of Nucleotides and Amino Acids.* New York: Wiley, 1960.
29. Brante, G. *Acta physiol. scandinav.* 18: Suppl. 63, 1949.
30. Brattgård, S.-O. *Acta radiol.* Suppl. 96, 1952.
31. Brattgård, S.-O. and H. Hydén. *Acta radiol.* Suppl. 94, 1952.
32. Brattgård, S-O. and H. Hydén. *Internat. Rev. Cytol.* 3: 455, 1954.
33. Brody, T. M. and J. A. Bain. *J. Biol. Chem.* 195: 685, 1952.
34. Brody, T. M., R. I. H. Wang and J. A. Bain. *J. Biol. Chem.* 198: 821, 1952.
35. Bumpus, F. M., H. Schwarz and I. H. Page. *Science* 125: 886, 1957.
36. Burgen, A. S. V. and L. M. Chipman. *J. Physiol.* 114: 296, 1951.
37. Burton, R. M. In: *Neurochemistry of Nucleotides and Amino Acids*, edited by R. O. Brady and D. B. Tower. New York: Wiley, 1960, p. 51.
38. Carter, H. E., D. C. Galanos and Y. Fujino. *Canad. J. Biochem. & Physiol.* 34: 320, 1956.
39. Christie, G. S., J. D. Judah and K. R. Rees. *Proc. Roy. Soc., London. ser. B* 141: 523, 1953.
40. Clark, D. D., M. J. Mycek, A. Neidle and H. Waelsch. *Arch. Biochem. & Biophys.* 79: 338, 1959.
41. Claude, A. *Harvey Lectures* 43: 121, 1947–48.
42. Close, H. G. *Biochem. J.* 27: 967, 1933.
43. Clouet, D. H. and D. Richter. *J. Neurochem.* 3: 219, 1959.
44. Cohen, B. S., F. W. Oberst, J. W. Crook and C. Harris. *J. Pharmacol. & Exper. Therap.* 116: 209, 1956.
45. Cornforth, J. W., M. E. Daines and A. Gottschalk. *Proc. Chem. Soc. (London)*, 1957, p. 25.
46. Dawson, R. M. C. and D. Richter. *Am. J. Physiol.* 160: 203, 1950.
47. Deluca, H. A., R. J. Rossiter and K. P. Strickland. *Biochem. J.* 55: 193, 1953.
48. Dounce, A. L., M. Morrison and K. J. Monty. *Nature, London* 176: 597, 1955.
48a. duBuy, H. G. *Neurology* 8, Suppl. 1: 69, 1958.
49. du Vigneaud, V., H. C. Lawler and F. A. Popenoe. *J. Am. Chem. Soc.* 75: 4880, 1953.
50. du Vigneaud, V., C. Ressler, J. M. Swan, C. W. Roberts and P. G. Katsoyannis. *J. Am. Chem. Soc.* 76: 3115, 1954.
51. Edström, J-E. *Biochim. et biophys. acta* 12: 361, 1953.
52. Edström, J-E. and H. Hydén. *Nature, London* 174: 128, 1954.
53. Ehrenberg, A. and H. Theorell. *Acta Chem. Scand.* 9: 1193, 1955.
54. Elliott, K. A. C. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955, p. 53.
55. Elliott, K. A. C. *Canad. J. Biochem. & Physiol.* 33: 466, 1955.

56. Elliott, K. A. C. and N. Henderson. *J. Neurophysiol.* 11: 473, 1948.
57. Engström, A. and D. Glick. *Science* 124: 27, 1956.
58. Engström, A. and H. Lüthy. *Exper. Cell Res.* 1: 81, 1950.
59. Feldberg, W. and M. Vogt. *J. Physiol.* 107: 372, 1948.
60. Fernandez-Moran, H. *Exper. Cell Res.* 3: 282, 1952.
61. Fernandez-Moran, H. In: *Metabolism of the Nervous System*, edited by D. Richter. London: Pergamon, 1957, p. 1.
62. Finean, J. B. *Exper. Cell Res.* 5: 202, 1953.
63. Finean, J. B. Cited by *Chem. Abstr.* 49: 1912d, 1955.
64. Finean, J. B., F. S. Sjöstrand and E. Steinmann. *Exper. Cell Res.* 5: 557, 1953.
65. Flexner, L. B. *Harvey Lectures* 47: 165, 1952.
66. Folch, J. *J. Biol. Chem.* 146: 35, 1942.
67. Folch, J. In: *Biology of Mental Health and Disease*. New York: Hoeber, 1952, p. 133.
68. Folch, J. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 121.
69. Folch, J., S. Arsove and J. A. Meath. *J. Biol. Chem.* 191: 819, 1951.
70. Folch, J. and F. N. LeBaron. *Fed. Proc.* 12: 203, 1953.
71. Folch, J. and F. N. LeBaron. *Canad. J. Biochem. & Physiol.* 34: 305, 1956.
72. Folch, J. and M. Lees. *J. Biol. Chem.* 191: 807, 1951.
73. Folch, J., M. Lees and G. H. Sloane-Stanley. In: *Metabolism of the Nervous System*, edited by D. Richter. London: Pergamon, 1957, p. 174.
74. Folch, J., J. A. Meath and S. Bogoch. *Fed. Proc.* 15: 254, 1956.
75. Folch, J. and W. C. Schneider. *J. Biol. Chem.* 137: 51, 1941.
76. Folch, J. and W. M. Sperry. *Ann. Rev. Biochem.* 17: 147, 1948.
77. Folch, J. and L. L. Uzman. *Fed. Proc.* 7: 155, 1948.
78. Folch, J. and D. W. Woolley. *J. Biol. Chem.* 142: 963, 1942.
79. Fraenkel-Conrat, H. *J. Am. Chem. Soc.* 78: 882, 1956.
80. Frohman, C. E., J. M. Orten and A. H. Smith. *J. Biol. Chem.* 193: 277, 1951.
81. Fukada, T. and G. B. Koelle. *J. Biophys. & Biochem. Cytol.* 5: 433, 1959.
82. Furst, S., A. Lajtha and H. Waelsch. *J. Neurochem.* 2: 216, 1958.
83. Gallagher, C. H., J. D. Judah and K. R. Rees. *Biochem. J.* 62: 436, 1956.
84. Geiger, A. and S. Yamasaki. *J. Neurochem.* 1: 93, 1956.
85. Geren, B. B. *Exper. Cell Res.* 7: 558, 1954.
86. Gerschenfeld, H. M., F. Wald, J. A. Zadunaisky and E. D. P. de Robertis. *Neurology* 9: 412, 1959.
87. Gersh, J. and D. Bodian. *J. Cell. & Comp. Physiol.* 31: 253, 1943.
88. Glees, P. *Neuroglia: Morphology and Function*. Springfield: Thomas, 1955.
89. Goldstein, L. and W. Plaut. *Proc. Nat. Acad. Sc., Washington* 41: 874, 1955.
90. Gordon, M. W. and J. I. Nurnberger. *Exper. Cell Res.* 8: 299, 1955.
91. Gore, M., F. Ibbott and H. McIlwain. *Biochem. J.* 47: 121, 1950.
92. Gore, M. B. R. and H. McIlwain. *J. Physiol.* 117: 471, 1952.
93. Gottschalk, A. *Physiol. Rev.* 37: 66, 1957.
94. Gurdjian, E. S., W. E. Stone and J. E. Webster. *A.M.A. Arch. Neurol. & Psychiat.* 51: 472, 1944.
95. Gurdjian, E. S., J. E. Webster and W. E. Stone. *Am. J. Physiol.* 156: 149, 1949.
96. Halliburton, W. D. *J. Physiol.* 15: 90, 1894.
97. Haurowitz, F. *Chemistry and Biology of Proteins*. New York: Acad. Press, 1950.
98. Heald, P. J. *Biochem. J.* 73: 132, 1959.
99. Heller, I. H. and K. A. C. Elliott. *Canad. J. Biochem. & Physiol.* 32: 584, 1954.
100. Heller, I. H. and K. A. C. Elliott. *Canad. J. Biochem. & Physiol.* 33: 395, 1955.
101. Hensing, J. T. *Cerebri Examen Chemicum, ex eodemque Phosphorum Singularem Omnia inflammabilia accendentem.* Giessen: Vulpii, 1719.
102. Hesselbach, M. L. and H. G. duBuy. *Proc. Soc. Exper. Biol. & Med.* 83: 62, 1953.
104. Hiatt, E. P. *Am. J. Physiol.* 129: 597, 1940.
105. Hild, W. and G. Zetler. *Experientia* 7: 189, 1951.
106. Hofmann, G. and H. Schinko. *Klin. Wchnschr.* 34: 86, 1956.
107. Hofmeister, F. *Die chemische Organisation der Zelle*. Braunschweig, 1901.
108. Hogeboom, G. H. and W. C. Schneider. *J. Biol. Chem.* 194: 513, 1952.
109. Hogeboom, G. H., W. C. Schneider and M. J. Striebich. *Cancer Res.* 13: 617, 1953.
110. Holland, W. C. and G. V. Auditore. *Am. J. Physiol.* 183: 309, 1955.
111. Holmes, E. G. *Biochem. J.* 26: 2005, 1932.
112. Holmes, J. H. and D. B. Tower. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H Page and J. H. Quastel. Springfield: Thomas, 1955, p. 262.
113. Hydén, H. *Acta physiol. scandinav.* 6: Suppl. 17, 1943.
114. Isselbacher, K. J., E. P. Anderson, K. Kurahashi and H. M. Kalckar. *Science* 123: 635, 1956.
115. Johnson, A. C., A. R. McNabb and R. J. Rossiter. *Biochem. J.* 43: 573, 1948.
116. Johnson, A. C., A. R. McNabb and R. J. Rossiter. *Biochem. J.* 43: 578, 1948.
117. Johnson, A. C., A. R. McNabb and R. J. Rossiter. *Biochem. J.* 44: 494, 1949.
118. Johnson, A. C., A. R. McNabb and R. J. Rossiter. *Biochem. J.* 45: 500, 1949.
119. Kalckar, H. M. *Science* 119: 479, 1954.
120. Kalckar, H. M., B. Braganca and A. Munch-Petersen. *Nature, London* 172: 1039, 1953.
121. Keller, E. B. and P. C. Zamecnik. *J. Biol. Chem.* 221: 45, 1956.
122. Kennedy, E. P. *Canad. J. Biochem. & Physiol.* 34: 334, 1956.
123. Kerr, S. E. *J. Biol. Chem.* 116: 1, 1936.
124. Kerr, S. E. and M. Ghantus. *J. Biol. Chem.* 116: 9, 1936.
125. Kety, S. S. In: *Metabolism of the Nervous System*, edited by D. Richter. London: Pergamon, 1957, p. 221.
126. Klatzo, I., A. Piraux and E. J. Laskowski. *J. Neuropath. & Exper. Neurol.* 17: 548, 1958.
127. Klein, J. R. and N. S. Olsen. *J. Biol. Chem.* 167: 747, 1947.
128. Klenk, E. *Ztschr. physiol. Chem.* 273: 76, 1942.
129. Klenk, E. *Ztschr. physiol. Chem.* 288: 216, 1951.
130. Klenk, E. *Ztschr. physiol. Chem.* 307: 266, 278, 1957.

131. Klenk, E. and H. Langerbeins. *Ztschr. physiol. Chem.* 270: 185, 1941.
132. Koch, W. and S. A. Mann. *J. Physiol.* 36: xxxvi, 1907.
133. Koelle, G. B. *J. Neuropath. & Exper. Neurol.* 14: 23, 1955.
134. Korey, S. R. (editor). *Progress in Neurobiology: IV. The Biology of Myelin.* New York: Hoeber, 1959.
135. Korey, S. R. and M. Orchen. *J. Neurochem.* 3: 277, 1959.
136. Kretchmer, N. and C. P. Barnum. *Arch. Biochem. & Biophys.* 31: 141, 1951.
137. Lehninger, A. L., C. L. Wadkins, C. Cooper, T. M. Devlin and J. L. Gamble. *Science* 128: 450, 1958.
138. Leövey, F. and E. Kerpel-Fronius. *Arch. exper. Path. u. Pharmakol.* 138: 372, 1929.
139. LePage, G. A. and W. C. Schneider. *J. Biol. Chem.* 176: 1021, 1948.
140. Littlefield, J. W. and E. B. Keller. *Fed. Proc.* 15: 302, 1946.
141. Logan, J. E., W. A. Manneli. and R. J. Rossiter. *Biochem. J.* 51: 470, 1952.
142. Lowe, I. P., E. Robins and G. S. Eyerman. *J. Neurochem.* 3: 8, 1958.
143. Lowry, O. H. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 350.
144. Lowry, O. H., D. R. Gilligan and E. M. Katersky. *J. Biol. Chem.* 139: 795, 1941.
145. Lowry, O. H. and A. B. Hastings. In: *Problems of Ageing* (2nd ed.), edited by E. V. Cowdry. Baltimore: Williams & Wilkins, 1942, p. 728.
146. Lowry, O. H., N. R. Roberts, K. Y. Leiner, M. L. Wu, A. L. Farr and R. W. Albers. *J. Biol. Chem.* 207: 39, 1954.
147. Luse, S. A. In: *Inhibition in the Nervous System and γ-Aminobutyric Acid*, edited by E. Roberts. London: Pergamon, 1960.
148. MacIntosh, F. C. *J. Physiol.* 99: 436, 1941.
149. Manery, J. F. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 124.
150. Manery, J. F. and A. B. Hastings. *J. Biol. Chem.* 127: 657, 1939.
151. Maxwell, E. S., H. M. Kalckar and R. M. Burton. *Biochim. et biophys. acta* 18: 444, 1955.
152. McGregor, H. H. *J. Biol. Chem.* 28: 403, 1916–17.
153. McIlwain, H. *Biochemistry and the Central Nervous System* (2nd ed.). Boston: Little, 1959.
154. McKhann, G. M. and D. B. Tower. *Am. J. Physiol.* 196: 36, 1959.
155. McKibben, J. M. and W. E. Taylor. *J. Biol. Chem.* 178: 17, 29, 1948.
156. Meyerhof, O. and J. R. Wilson. *Arch. Biochem.* 14: 71, 1947.
157. Nurnberger, J. I. *A. Res. Nerv. & Ment. Dis., Proc.* 32: 132, 1953.
158. Nurnberger, J. I. In. *Biology of Neuroglia*, edited by W. F. Windle. Springfield: Thomas, 1958, p. 193.
159. Nurnberger, J. I., A. Engström and B. Lindström. *J. Cell. & Comp. Physiol.* 39: 215, 1952.
160. Nygaard, A. P. and J. B. Sumner. *J. Biol. Chem.* 200: 723, 1953.
161. Oberst, F. W. and M. K. Christensen. *J. Pharmacol. & Exper. Therap.* 116: 216, 1956.
162. Ochoa, S. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 97.
163. Ochoa, S. and R. J. Rossiter. *Biochem. J.* 33: 2008, 1939.
164. Olsen, N. S. and D. H. Clouet. *Fed. Proc.* 15: 323, 1956.
165. Olsen, N. S. and J. R. Klein. *A. Res. Nerv. & Ment. Dis., Proc.* 26: 118, 1946.
166. Olsen, N. S. and J. R. Klein. *J. Biol. Chem.* 167: 739, 1947.
167. Paasonen, M. K. and M. Vogt. *J. Physiol.* 131: 617, 1956.
168. Page, I. H. *Chemistry of the Brain.* Springfield: Thomas, 1937.
169. Palade, G. E. *J. Histochem.* 1: 188, 1953.
170. Palade, G. E. and S. L. Palay. *Anat. Rec.* 118: 335, 1954
171. Palade, G. E. and P. Siekevitz. *J. Biophys. & Biochem. Cytol.* 2: 171, 1956.
172. Palay, S. L. In: *Biology of Neuroglia*, edited by W. F. Windle. Springfield: Thomas, 1958, p. 24.
173. Palay, S. L. and G. E. Palade. *J. Biophys. & Biochem. Cytol.* 1: 69, 1955.
174. Palladin, A. and W. Bjeljaewa. *Ztschr. physiol. Chem.* 141: 33, 1924.
175. Palladin, A. and D. Zuwerkalow. *Ztschr. physiol. Chem.* 139: 57, 1924.
176. Pappius, H. and K. A. C. Elliott. *Canad. J. Biochem. & Physiol.* 32: 484, 1954.
177. Pope, A. *J. Neurophysiol.* 15: 115, 1952.
178. Pope, A. *J. Neuropath. & Exper. Neurol.* 14: 39, 1955.
179. Pope, A. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 341.
180. Pope, A., W. Caveness and K. E. Livingston. *A. M. A. Arch. Neurol. & Psychiat.* 68: 425, 1952.
181. Price, J. M., E. C. Miller and J. A. Miller. *J. Biol. Chem.* 173: 345, 1948.
182. Randall, L. O. *J. Biol. Chem.* 124: 481, 1938.
183. Rapport, M. In: *Progress in Neurobiology: IV. The Biology of Myelin*, edited by S. R. Korey. New York: Hoeber, 1959, p. 282.
184. Rich, A. In: *Progress in Neurobiology: I. Neurochemistry*, edited by S. R. Korey and J. I. Nurnberger. New York: Hoeber, 1956, p. 114.
185. Richter, D. and R. M. C. Dawson. *Am. J. Physiol.* 154: 73, 1948.
186. Richter, D. and R. P. Hullin. *Biochem. J.* 48: 406, 1951.
187. Roberts, E. In: *Progress in Neurobiology: I. Neurochemistry*, edited by S. R. Korey and J. I. Nurnberger. New York: Hoeber, 1956, p. 11.
188. Roberts, E. (editor). *Inhibition in the Nervous System and γ-Aminobutyric Acid.* London: Pergamon, 1960.
189. Robins, E., K. M Eydt and D. E. Smith. *J. Biol. Chem.* 220: 677, 1956.
190. Robins, E. and D. E. Smith. *A. Res. Nerv. & Ment. Dis., Proc.* 32: 305, 1953.
191. Robins, E., D. E. Smith and K. M. Eydt. *J. Neurochem.* 1: 54, 1956.
192. Robins, E., D. E. Smith and K. M Eydt. *J. Neurochem.* 1: 77, 1956.
193. Robins, E., D. E. Smith, K. M. Eydt and R. E. McCaman. *J. Neurochem.* 1: 68, 1956.
194. Rossiter, R. J. In: *Neurochemistry*, edited by K. A. C.

Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955, p. 11.
195. Rossiter, R. J. *Canad. J. Biochem. & Physiol.* 35: 579, 1957.
196. Rossiter, R. J., W. Thompson and K. P. Strickland. In: *Neurochemistry of Nucleotides and Amino Acids*, edited by R. O. Brady and D. B. Tower. New York: Wiley, 1960, p. 28.
197. Rozsa, G., C. Morgan, A. Szent-Györgyi and R. W. G. Wyckoff. *Biochim. et biophys. acta* 6: 13, 1950.
198. Salvador, R. A. and R. W. Albers. *J. Biol. Chem.* 234: 922, 1959.
199. Sanadi, D. R., D. M. Gibson, P. Ayengar and M. Jacob. *J. Biol. Chem.* 218: 505, 1956.
200. Scharrer, E. and B. Scharrer. In: *Handbuch der Mikroskopischen Anatomie des Menschen*, edited by W. von Möllendorff. Berlin: Springer, 1954, vol. 6, p. 953.
201. Schmidt, W. J. *Ztschr. wiss. Mikroskop.* 54: 159, 1937.
202. Schmitt, F. O. *Biol. Rev.* 14: 27, 1939.
203. Schmitt, F. O. *A. Res. Nerv. & Ment. Dis., Proc.* 28: 247, 1949.
204. Schmitz, E. In: *Handbuch der Normalen und Pathologischen Physiologie*, edited by A. Bethe, G. von Bergmann, G. Embden and A. Ellinger. Berlin: Springer, 1929, vol. 9, p. 47.
205. Schneider, W. C. *J. Histochem.* 1: 212, 1953.
206. Schneider, W. C. and G. H. Hogeboom. *Cancer Res.* 11: 1, 1951.
207. Shariff, G. A. *J. Comp. Neurol.* 98: 381, 1953.
208. Siekevitz, P. *J. Biol. Chem.* 195: 549, 1952.
209. Siekevitz, P. In: *Regulation of Cell Metabolism*, edited by G. E. W. Wolstenholme and C. M. O'Connor. Boston: Little, 1959, p. 17.
210. Spiro, M. J. and J. M. McKibben. *J. Biol. Chem.* 219: 643, 1956.
211. Stanbury, W. S. and G. H. Mudge. *Proc. Soc. Exper. Biol. & Med.* 82: 675, 1953.
212. Stewart-Wallace, A. M. *Brain* 62: 426, 1939.
213. Stone, W. E. *J. Biol. Chem.* 135: 43, 1940.
214. Stone, W. E., J. E. Webster and E. S. Gurdjian. *J. Neurophysiol.* 8: 233, 1945.
215. Strickland, K. P. *Canad. J. Med. Sci.* 30: 484, 1952.
216. Strominger, J. L. and O. H. Lowry. *J. Biol. Chem.* 213: 635, 1955.
217. Swanson, M. A. and C. Artom. *J. Biol. Chem.* 187: 281, 1950.
218. Tallan, H. H. *Fed. Proc.* 15: 368, 1956.
219. Tallan, H. H., S. Moore and W. H. Stein. *J. Biol. Chem.* 211: 927, 1954.
220. Tallan, H. H., S. Moore and W. H. Stein. *J. Biol. Chem.* 219: 257, 1956.
221. Thomas, J. and H. McIlwain. *J. Neurochem.* 1: 1, 1956.
222. Thudichum, J. L. W. *A Treatise on the Chemical Constitution of the Brain*. London: Baillière, Tindall & Cox, 1884.
223. Thudichum, J. L. W. *Die Chemische Konstitution des Gehirns des Menschen und der Tiere*. Tübingen: Pietzcker, 1901.
224. Toschi, G. *Exper. Cell Res.* 16: 232, 1959.
225. Tower, D. B. *J. Comp. Neurol.* 101: 19, 1954.
226. Tower, D. B. *Neurology* 5: 113, 1955.
227. Tower, D. B. In: *Progress in Neurobiology: I. Neurochemistry*, edited by S. R. Korey and J. I. Nurnberger. New York: Hoeber, 1956, p. 169.
228. Tower, D. B. *Am. J. Clin. Nutrition* 4: 329, 1956.
229. Tower, D. B. *Neurology* 8, Suppl. 1: 3, 1958.
230. Tower, D. B. In: *Biochemistry of the Central Nervous System*, edited by F. Brücke. London: Pergamon, 1959, p. 213.
231. Tower, D. B. In: *Neurochemistry of Nucleotides and Amino Acids*, edited by R. O. Brady and D. B. Tower. New York: Wiley, 1960, p. 173.
232. Tower, D. B. In: *Structure and Function of the Cerebral Cortex*, edited by J. P. Schadé and D. B. Tower. Amsterdam: Elsevier, 1960.
233. Tower, D. B. and K. A. C. Elliott. *Am. J. Physiol.* 168: 747, 1952.
234. Tupikova, N. and R. W. Gerard. *Am. J. Physiol.* 119: 414, 1937.
235. Tyrrell, L. W. and D. Richter. *Biochem. J.* 49: li, 1951.
236. Vauquelin, L. N. *Ann. Muséum d'Histoire naturelle* 18: 212, 1811.
237. Victor, J. V. and A. Wolf. *A. Res. Nerv. & Ment. Dis., Proc.* 16: 44, 1935.
238. Vincent, W. S. *Internat. Rev. Cytol.* 4: 269, 1955.
239. Vladimirov, G. E. and L. N. Rubel. In: *Metabolism of the Nervous System*, edited by D. Richter. London: Pergamon, 1957, p. 263.
240. Vogt, M. *J. Physiol.* 123: 451, 1954.
241. Waelsch, H. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955, p. 173.
242. Waelsch, H. (editor). *Biochemistry of the Developing Nervous System*. New York: Acad. Press, 1955.
243. Waelsch, H. (editor). *Progress in Neurobiology: II. Ultrastructure and Cellular Chemistry of Neural Tissue*. New York: Hoeber, 1957.
244. Waelsch, H. In: *Neurochemistry of Nucleotides and Amino Acids*, edited by R. O. Brady and D. B. Tower. New York: Wiley, 1960, p. 205.
245. Waelsch, H. In: *Structure and Function of the Cerebral Cortex*, edited by J. P. Schadé and D. B. Tower. Amsterdam: Elsevier, 1960.
246. Weil, A. *Ztschr. physiol. Chem.* 89: 349, 1914.
247. Weil-Malherbe, H. *Biochem. Soc. Symposia (Cambridge, Engl.)* 8: 16, 1952.
248. Windle, W. F. (editor). *Biology of Neuroglia*. Springfield Thomas, 1958.
249. Winterstein, H. In: *Handbuch der Normalen und Pathologischen Physiologie*, edited by A. Bethe, G. von Bergmann, G. Embden and A. Ellinger. Berlin: Springer, 1929, vol. 9, p. 515.
250. Wolstenholme, G. E. W. and C. M. O'Connor (editors). *Regulation of Cell Metabolism*. Boston: Little, 1959.
251. Woodbury, D. M. In: *Biology of Neuroglia*, edited by W. F. Windle. Springfield: Thomas, 1958, p. 120.
252. Yannet, H. and D. C. Darrow. *J. Biol. Chem.* 123: 295, 1938.

CHAPTER LXXV

# Neuronal metabolism[1,2]

L. G. ABOOD | *Departments of Psychiatry and Biochemistry, University of Illinois College of Medicine, Chicago, Illinois*

CHAPTER CONTENTS



UNTIL THE LAST DECADE any attempt to discuss the problem of 'neuronal' metabolism was either burdened with speculation or completely destined to failure, primarily because the concept of the 'neuron' was not sufficiently delineated from a chemical or biochemical point of view. With the application of highly refined microchemical and microphysical techniques to the chemistry of the single cell, not only has it been possible to obtain information about the chemistry of the adult neuron at rest, but considerable knowledge is accumulating on the biochemical changes during growth and activity, as well as under pharmacological and pathological conditions. Although the neuron comprises the main functional unit of the nervous system, morphologically it is embedded in a syncytium of neuroglial elements, the biochemical and even functional role of which remains obscure. To what extent the chemistry and function of the neuron is related to the neuroglial components is a problem in itself, but the necessity for studying each cell type individually remains acute.

Even in the case of 'peripheral nerve,' the contribution of connective tissue and endoneurial elements to the overall chemistry must not be overlooked. There is a further consideration which concerns the exact role of the extraneuronal elements of neural tissue. As long as the mechanism of excitation and conduction remains a problem, the question of the extent of involvement of the neuroglial elements will remain open. For this reason it is equally as dangerous to exclude the neuroglia from a discussion of 'neuronal' chemistry as it is to interpret the chemistry of neuronal function on the basis of the chemistry of the heterogeneous complex of the nervous system. The need for distinguishing the metabolism and chemistry of the functional elements from the merely structural or passive components is tantamount to an understanding of the relationship of chemistry to function. In many species and under certain conditions the evidence that the neuron itself is autonomously functional in excitation is overwhelming, so that some justification does exist for studying 'neuronal chemistry' per se.

It seems highly improbable, however, that the role of the neuroglial elements is a purely 'passive' one. Early in this century Nageotte (87) suggested that the function of the neuroglia was a nutritive one insofar as it appeared to contain secretory granules. A similar view still obtains today, particularly in regard to invertebrate nerves where the nutritional state of the neurons is correlated with the density of secretion granules within the neuroglia, a function which may be of special significance since blood

[1] The unpublished work was supported by a contract from the Office of Naval Research.

[2] The purpose of this chapter is not to present a comprehensive review of the biochemistry of the nervous system, but rather to indicate general trends and, wherever possible, to relate neurochemistry to neural function. For more extensive biochemical details, the reader is referred elsewhere (27, 63, 95, 118).

TABLE 1. *Activity of Respiratory Enzyme Systems in Various Cell Types of Mammalian Nervous System* †*

| Structure | Sources | Oxid. $Q_{O_2}$‡ | Glyc. $Q^{N_2}_{CO_2}$§ | Malic Dehyd. | Aldolase | ATPase | ChExt. | Cyt. Oxid. | Glut. Dehyd. |
|---|---|---|---|---|---|---|---|---|---|
| Dendrites | Ammon's horn | 16 | 55 | 57 | 4.0 | 4.8 | 1.3 | 9.7 | 2.3 |
| | Cerebellum | | | 55 | | | | | |
| | Cerebrum | | | | | | | | |
| Neuron soma | Ammon's horn | 13 | 48 | 55 | 2.7 | 3.8 | 1.6 | 11.2 | 3.0 |
| | Cerebellum | 13 | 50 | 60 | | | | | |
| | Cerebrum | | | | | | | | |
| Neuroglia | Cerebrum | 10 | 35 | | 3.1 | 3.8 | 1.7 | | |
| Axon (CNS) | Ammon's horn | 4 | 13 | 25 | 2.7 | 2.7 | 1.3 | 3.0 | 0.26 |
| | Cerebellum | | | 20 | | | | | |
| | Corpus collosum | | | | | | | | |
| Axon (peripheral) | Optic | 0.7 | 2.5 | 5.0 | 0.15 | 3.5 | 1.0 | 0.5 | |
| | Sciatic | | | 2.0 | | | | | |
| Average brain | | 14 | 52 | | 3.5 | 5 | 2.5 | | 5.1 |
| Neurons (tissue culture) | Cerebrum | 15 | 48 | 52 | | 4.0 | | 10.0 | 2.2 |
| Neuroglia (tissue culture) | Cerebrum | 14 | 42 | 44 | | 3.1 | | 10.2 | |

* See text for references.

† Activity is expressed in mmole of substrate utilized per gm dry wt. per hr. at 37 °C.

‡ $\mu$mole $O_2$ utilized per mg dry wt. per hr.

§ $\mu$mole $CO_2$ liberated per mg dry wt. per hr.

vessels are generally absent from the central nervous system in invertebrates (50). Electronmicroscopy has revealed the existence of fine granules (0.1 to 0.5 $\mu$) within neuroglia which occasionally are found in large clusters as if they were in the process of being discharged into the intracellular space (103). The nerve cell bodies of the invertebrate nervous system also appear to contain secretory-like inclusions of varying sizes in close association with the 'Golgi' complex or a double-layered endoplasmic reticulum (24).

### CYTOCHEMISTRY

With the development of histochemical and refined microchemical techniques, a considerable amount of information has accumulated on the localization of enzymes and other chemical substances within the neuron as well as on the differentiation of neuronal chemistry from the complex interrelationship of the nonneuronal elements. Although histological evidence is scanty, it appears as though most of the gray matter of the brain is comprised of dendritic processes and that the perikarya and glia comprise less than 10 per cent of the total mass (115). In most mammalian species an estimate of 5 per cent for the total mass of nerve cell bodies in whole brain would be somewhat high (115).

By means of ultramicrochemical techniques it has been possible to study the metabolism of distinct types of cell populations in the hippocampal and cerebral cortex of rabbit brain (78, 92, 106, 110). (See table 1.) Such enzymes as the dehydrogenases (110) and cytochrome oxidase (92, 93) seem to be richest in the layers containing pyramidal cell bodies and dendritic processes, while aldolase and adenosinetriphosphatase have a more random distribution throughout the cortex. In many regions of the brain such as the cerebral and cerebellar cortex there is some justification, therefore, for believing that

'brain metabolism' is in essence largely 'dendritic metabolism' (79).

In the case of hypothalamic tissue, the oxidative and glycolytic metabolism of the supraoptic and paraventricular nuclei does not differ greatly from that of the surrounding tissue (108, 110). Certain fiber tracts such as the nonmyelinated tract in Ammon's horn and the optic tract are especially rich in lactic and malic dehydrogenase, as are the dendrites, while, in contrast, glutamic dehydrogenase is highest in myelinated nerves and the molecular layer of Ammon's horn (110). Aldolase activity parallels malic and lactic dehydrogenase in the Ammon's horn as well as in myelinated fibers and the optic tract.

Among other enzymes which are present in appreciable quantities in white matter are adenosinetriphosphatase (6, 7, 88, 100) and particularly purine nucleoside phosphorylase (101). Studies on the cytoarchitectonic pattern of enzymes in the rat cerebral cortex have served in part to correlate particular enzyme systems with neural cell types. The distribution of many respiratory enzymes and phosphatases appears to be related to the protein content in the various layers of the cerebral cortex and to be a mirror image of the lipid concentration (98, 100). The distribution of dipeptidase correlates with the pattern density of neuronal and neuroglial cell bodies, while acetylcholinesterase parallels the distribution of the axons and dendrites, including their ramifications (16). Acetylcholinesterase seems to be associated to a considerable extent with motor end plates and perhaps other synapses (16, 71); and, although its appearance embryologically is correlated with the development of neurons (45), it is also present in large amounts in white matter (54, 57). A porphyrin (probably coproporphyrin) has been found exclusively in the white matter, and largely in oligodendroglia (69). The reason for the existence of porphyrins in the brain is not at all clear, but they are believed to be involved in the photostimulation of mammalian and avian sexual cycles, so that the central nervous system itself may actually be a 'tissue of perception' (35, 91).

The retina is particularly useful for studying the quantitative histochemistry of neural tissue since the various components of the neuron are discreetly separated in this structure (80). Malic dehydrogenase and transaminase (80, 120), as well as succinoxidase, are especially concentrated in the layer consisting of the inner segments of rods, an area which is extremely dense in mitochondria (107). Lactic dehydrogenase and phosphoglucoisomerase, which appear to have a reciprocal relationship to malic dehydrogenase and which are indicative of overall glycolytic metabolism, are especially concentrated in all the inner layers of the rabbit retina (80). The outer segments of the rods and cones are deficient in all of the enzymes mentioned above, suggesting that, perhaps, these structures are metabolically dependent upon adjacent layers (80). In general, the activity of isomerase and malic and lactic dehydrogenase isomerase was several times greater in retina than that in whole brain, whereas glutamic-aspartic transaminase was considerably lower.

## MITOCHONDRIA

As the neuroblast is transformed into the adult neuron and the nervous system begins to exhibit functional characteristics, a number of dramatic changes in its enzymatic pattern take place. With the appearance of the dehydrogenases, cytochrome oxidase, adenosinetriphosphatase and other mitochondrial enzymes, the main pathway of metabolic energy shifts from anaerobiosis to aerobic glycolysis, thereby tremendously increasing the 'efficiency' of energy production. In the early embryonic development of the neuron most of the nuclei have presumably reached maturation, as indicated by its high DNA content; and with the development of cytoplasm and dendrites one would expect a corresponding increase in the mitochondrial population.

With the demonstration that oxidative phosphorylation of all tissues, including brain (4, 18) and peripheral nerve (6), is carried on by the mitochondria, the problem of energy production within the neuron and its localization has been placed in a new perspective. The concept that mitochondria are the sites of energy production within the nerve originated almost a half century ago (87), and neuroanatomists since that time have been concerned with their intraneuronal distribution. [See Abood & Gerard (6) for review.] Mitochondria are most abundant in the nerve cell body and dendrites, and although present throughout the axoplasm and neurilemmal sheath, they are concentrated in certain functionally significant areas such as the Schwann cell (87), nodes of Ranvier (37), at the terminal boutons (13), and the general area of the myoneural junction (13). Quantitative data on mitochondrial distribution in neural tissue is lacking, although a correlation has been found between mitochondrial

TABLE 2. *Distribution of Enzymes in Rat Brain**

| Cell Fraction† | Tissue Studied | Enzymes |
|---|---|---|
| Nuclei | Gray cortex | Acid phosphatases<br>Alkaline phosphatases<br>Aldolase |
| Mitochondria | Gray cortex<br>Spinal white<br>Peripheral nerve<br>Hypothalamus | Hexokinase<br>Tricarboxylic cycle dehydrogenases<br>Cytochrome oxidase<br>Oxidative phosphorylation<br>Adenylic kinase<br>'$\beta$-Hydroxybutyric' oxidase<br>ATPase-$Ca^{++}$ activated<br>Transphosphorylases<br>DNP-cytochrome C reductase<br>$^1_3$ Glycolytic enzymes |
| Microsomes | Gray cortex<br>Spinal white<br>Peripheral nerve<br>Hypothalamus | Adenylic deaminase<br>Adenylic kinase<br>ATPase-$Mg^{++}$ activated<br>Glutathione reductase<br>Cholinesterase |
| Soluble proteins | Gray cortex<br>Spinal white<br>Peripheral nerve | $^2_3$ Glycolytic enzymes<br>Amine oxidase |

* Data from references (1, 2, 5, 7, 8, 17, 80, 99).
† Intracellular fractions obtained through differential centrifugation.

content and oxidative activity of various nerve fibers of the central and peripheral nervous system (unpublished observations). With regard to glia, information regarding mitochondrial concentration and distribution is almost completely lacking. Oligodendroglia have high oxidative activity (100), while the metabolic activity of astrocytes and microglia can only be inferred from studies on white matter. In addition to being the primary source of energy production, the mitochondria accumulate many important neurohumoral agents, such as epinephrine (53), norepinephrine (unpublished observations), histamine (21) and 5-hydroxytryptamine (unpublished observations). Both the nature and significance of the binding of these agents are entirely unknown, although, in view of the potent pharmacological effect of these agents on smooth muscle, one might suspect their possible relationship to mitochondrial physiology. Furthermore, the fact that neurohumoral transmission has been established at the nerve endings (30), where mitochondria are especially concentrated, points to an important relationship between mitochondria and such agents. Oxidative phosphorylation itself, however, does not appear to depend upon the presence of the neurohumoral agents within mitochondria (unpublished observations). The recent finding that the pulsatile activity of oligodendroglia is influenced by 5-hydroxytryptamine is suggestive of the role of this neurohumor in the regulation of secretion or fluid transport (121).

From studies with mammalian nerve and glia cells grown in tissue cultures, it appears that not only is the oxidative and glycolytic activity of microglia and oligodendroglia of considerable magnitude, the $Q_{O_2}$ varying from 15 to 20 (2), but in the case of certain enzymes, such as cytochrome oxidase, succinic and malic dehydrogenases, and adenosinetriphosphatase, the activity of glia is about one half to two thirds that of neurons (unpublished observations). It is, however, difficult at present to compare quantitatively the metabolic activity of cells grown in tissue culture with the parent cells in their natural environment, a problem confronting all *in vitro* work insofar as normally present physical and chemical regulatory factors are eliminated or interfered with in disrupted tissues.

## MYELINIZATION

From a study of the formation of various lipids and related substances in mouse brain during embryonic development, an attempt has been made to correlate structural and functional development with chemical composition (34). Before the onset of myelinization at about the 7th day, the brain has attained 60 per cent of its adult weight, 40 per cent of the proteins, 50 per cent of the strandin and 30 per cent of the phosphatides. With the development of myelinization, dendritic aborization and neuroglia occurs a rapid formation of proteolipids, cerebrosides, cholesterol and acetal phosphatides. Since these lipids were either almost or completely absent before myelinization, it would appear that their formation is a measure of 'white matter events,' while strandin may be taken as an index of the development of 'grey matter.' Sphingomyelin has been shown to be almost exclusively associated with the nerve sheath and is likewise absent before myelinization (105). By the end of the stage of myelinization, the sphingolipids have increased to such an extent that they comprise almost half of the total lipids in brain and spinal cord (34). Gangliosides, on the other hand, are associated with neuronal soma and dendrites (68). It appears as though cerebrosides, cholesterol and sphingomyelins, rather than cephalins and lecithins, constitute the lipids of the myelin sheath (65). By the application of microchemical techniques to the quantitative histochemistry of brain, it has been shown that in the white matter of the cerebellar cortex (98, 100) and cerebral cortex (99) the cephalins (probably phosphatidylserines rather than phosphatidylethanolamines) are quantitatively similar to the sphingolipids. In the cerebral cortex the nonphosphorus-containing sphingolipids appear to be the most characteristic lipid of white matter (99, 105), these lipids being found in surprisingly low concentrations in the molecular layers (largely dendritic).

In recent years, a number of fine physicochemical tools have been used in an attempt to determine the structure of myelin. Polarization and x-ray diffraction studies have revealed myelin to consist of a laminated lipoprotein structure (32, 104). The fatty acid chains of the complex are oriented radially, and the repeating periods of the lipoprotein are amazingly constant (about 180 Å) from species to species. The lipoid portion in itself has a laminar structure comprised of a complex of unesterified cholesterol and phospholipid (31). By means of infrared spectrophotometry it is possible to distinguish between certain hydrocarbon groups, such as $CH_2$ and $CH_3$, within myelin preparations (22). Such analysis permits, among other things, the determination of the deposition of fatty acid in myelin as well as the synthesis of long chain fatty acids from shorter ones. It has also been possible to follow the deposition of myelin in the developing nervous system.

Myelination proceeds as a layer-by-layer addition of lipid-protein complexes originating from the infolding of the surface membrane of the Schwann cell. Attached to the inner layers as outpocketings into the axoplasm of the spiraling-like structure are numerous mitochondria which are believed either to result from the Schwann cell surface or to be actively engaged in myelinization (46, 47). By means of polarization optics, the neurofibrils of the axoplasm appear to consist of asymmetric submicroscopic particles oriented parallel with the fiber axis (12). The composition of the submicroscopic particles is not known, although they are believed to be microsomes (10) which can be separated from nerve as a heterogeneous group of spherical particles which are 10 to 200 mμ in diameter (6, 10). In addition to their property of birefrigence of flow and ability to readily form bead-like threads, the microsomes are rich in enzymes involved in the splitting of adenine nucleotides, a readily available source of energy (10).

## STRUCTURAL ELEMENTS, GROWTH AND DIFFERENTIATION

Among the most promising techniques used in the study of intracytoplasmic chemistry of brain are those of ultraviolet microspectography (28) and x-ray microradiography (29). The methods have been used in the study of lipids, ribose nucleic acid (RNA) and proteins in single neurons from Deiter's nucleus, spinal ganglia and Purkinje cells. The neurons of Deiter's nucleus are characterized by large amounts of lipids and RNA, the lipids comprising about 56 per cent of the total weight ($10^{-9}$ mg per $\mu^3$) of a cell and RNA about 25 per cent (17). Purkinje cells contain less than 5 per cent RNA and about 20 per cent lipids, while the protein content appears to differentiate the cells into three distinct classes. Spinal ganglia contain about 1 per cent RNA and one half the lipid content of the Deiter's or Purkinje cells. This considerable variation in the lipid and RNA composition of different nerve cells is rather surprising and suggests strongly the need for further differentiation of neural chemistry with respect to

cell type. Since about 30 per cent of the brain lipids are associated with mitochondria and most of the RNA with microsomes (4), the interesting possibility offers itself that the Deiter's cells, among the largest of neurons, are richest in mitochondria and microsomes. Purkinje cells would, then, have somewhat fewer mitochondria and considerably less microsomes, while spinal ganglia would contain the least of both particulates. Such speculation is not in conflict with observations from other sources concerning the respiratory metabolism of these cells.

With the loss of function during degeneration of the severed peripheral nerve, there are a series of characteristic changes which have provided some important clues to the understanding of neuronal metabolism. After nerve section certain nonspecific phosphatases decreased rapidly until the 16th day following section, while nucleotidase and $\beta$-glucuronidase increased considerably after either nerve section or crush, the RNA increasing at a greater rate than the DNA (58, 59). Phospholipids remain unchanged after either section or crush until the 8th day when they began to rapidly decrease (77). While the phospholipid continued to decrease in the sectioned nerve after 30 days, it began to gradually increase in the crushed nerve throughout the period of regeneration when remyelinization was occurring. These results are indicative of the fact that protein, lipid and nucleic acid breakdown and synthesis do occur in adult neural tissue and at a surprisingly rapid rate. The inability to demonstrate noncarbohydrate pathways of metabolism in neural tissue *in vitro* is particularly acute in the light of such studies. Perhaps the metabolic processes during Wallerian degeneration involve a transient reversion to the embryonic development of peripheral nerve, and with regeneration completed the enzymatic processes, initially elaborated by the RNA and DNA of proliferating Schwann cells, become dormant once more. The important fact is that neural tissue does contain such metabolic systems that can be called into play to suit its requirements. Very likely these processes are under the control of certain regulatory mechanisms which in turn are responsive to particular physicochemical stimuli, such as trauma and excitatory activity. In all cells throughout the organism, enzymes and structural components are constantly being resynthesized and, although mitotic activity in the neurons presumably ceases after maturation of the neuroblast, neural tissue must certainly be no exception. Protein synthesis proceeds at a rapid rate even in the adult brain, as indicated by experiments with methionine-$S^{35}$ (36).

Insofar as long axons may contain a thousand times as much protoplasm as the cell soma, during axonal regeneration the soma must produce several times its protoplasmic volume per day (43). Among the most challenging problems of neurochemistry is that concerned with the factors initiating and regulating the regenerative processes of the dissevered axon. Numerous explanations have been offered for neurogenesis and, although the discussion is beyond the scope of this chapter, it is important to mention some of the neurotropic substances that are presumably involved. Fragments of mouse sarcoma, but not of brain or liver, were found to stimulate selectively the growth and differentiation of sympathetic and sensory neurons (74). Chemical isolation and characterization of the neurotropic agent revealed the following composition: 66 per cent protein, 27 per cent RNA and 0.2 per cent DNA. The agent, therefore, is either a specific protein associated with microsomal RNA or, if it is RNA, it must be a particular form of the nucleic acid found in sarcoma but not in normal brain or liver. The observation that neuronal growth and proliferation in the mesencephalic nucleus of amphibians increased abruptly during metamorphosis led to the finding that thyroxine was the agent responsible for this sudden maturation (72). The collateral branching of the intact uninjured nerve occurring after the innervated muscle is rendered paretic has been attributed to the elaboration of a substance containing unsaturated (glyceride) fatty acids (20). The facilitation of neuronal growth in tissue cultures by cortisone (40, 40a) and of nerve regeneration in the transected spinal cord by Piromen (a bacterial polysaccharide) (40, 40a) have led to the development of the notion that nerve regeneration is normally prevented by glial proliferation which is presumably inhibited by these substances.

The numerous and unique structural changes occurring in the axoplasm and cell body during growth and differentiation provide a fruitful basis for approaching the problem of neural function in relation to chemistry. Perhaps the most important structures to undergo disintegration after section of the axon are the neurofibrils which presumably constitute the core of the conductive apparatus (102). The surrounding 'neuroplasm,' meanwhile, establishes contact with elements of the neurilemmal sheath and eventually forms the protoplasmic bands of Beungner which constitute the framework for the neurofibrils during regeneration (14, 94). Protoplasm is con-

tinuously flowing from the cell body down the axon, but in such a way that the many chemical events are inextricably bound to the re-establishment of neural function (119). If the neurofibrils are comprised of the microsomal particles, as, apparently, are the cytoplasmic fibrils of other cells (84, 85), the high ATPase and nucleotide metabolism (10) of the microsomes are suggestive of the notion that the neurofibrils are in a constant state of activity (10, 84). Insofar as protein synthesis is also linked to RNA, a microsomal constituent, the problem of enzymatic and structural regeneration is linked to function.

## SUBSTRATES OF THE NEURON

Although there is little doubt that glucose is the chief substrate of the central nervous system during rest and activity, the problem with regard to peripheral nerve is considerably more complex. Nerve appears to contain the enzyme systems involved in glycolysis and oxidation via the Krebs' cycle, but the evidence to suggest that carbohydrate is the main substrate either during rest or activity is not entirely adequate. Among the noncarbohydrate substrates that are utilized by neural tissues are amino acids (1, 86), fatty acids (1, 11, 15, 42) and nucleic acids constituents (3, 39), although little is known of their relative importance in comparison to carbohydrates. Glutamic acid, for example, is utilized as readily by mitochondria of brain (7, 18) and nerve (6) as is pyruvate and, furthermore, contributes to more efficient phosphorylation (i.e. with higher P O ratios) than does pyruvate (9). This amino acid is present in significant amounts in nerve (75) as well as brain; and insofar as it comprises an intimate link between protein and carbohydrate metabolism in addition to being important to function (117), its possible metabolic role deserves more exploration.

In the case of peripheral nerve it seems indisputable that the metabolism during activity is different from that at rest. A specific inhibitor of the Krebs' cycle, methyl fluoracetate, can depress the resting metabolism to less than half while leaving unaffected the extra oxygen consumption of tetanization; conversely, sodium azide abolishes the extra oxidation of activity while not affecting resting metabolism (25). With the use of isotopically labeled amino acid and carbohydrates, it has been shown that acetate and glucose metabolism during excitation of peripheral nerve actually fall below the resting level, whereas the metabolism of amino acids, such as glutamate, alanine and glycine, increases significantly (86). Certain proteins from frog sciatic nerve, which appear to be proteolipids (unpublished observations), show an actual increase during excitation while decreasing during ether anesthesia. These proteolipids contain proportionately large amounts of glutamate, aspartate and alanine, amino acids which, in the free form, decrease during stimulation (unpublished observations). Insofar as nucleic acid constituents of nerve, such as cytosine, guanine and adenine, also decrease during stimulation, it appears likely that a liponucleoprotein complex, described by Folch (33), is being degraded during activity, and that the 'proteolipids' are released as a consequence (unpublished observations).

Although glucose is the chief fuel of the brain, there are conditions under which noncarbohydrate substrates are apparently utilized. The suggestion that neural tissue is able to utilize lipids was made by Gerard (42) many years ago, but additional evidence was not forthcoming until recently. A perfused preparation of cat brain is able to survive with apparently normal metabolism and functional activity for at least 2 hr. without glucose or other exogenous substrates (38). In the absence of glucose the brain is able to degrade its own structural components, such elements as the 'microsomes' and soluble proteins of the cerebral cortex falling to 50 per cent of their normal value before functional failure of the preparation (3).

Until quite recently, attempts to demonstrate fatty acid oxidation in neural tissues have been largely unsuccessful. Of the numerous and short-chain fatty acids tested, $\beta$-hydroxybutyrate appears to be the only one oxidized by brain or nerve homogenates and mitochondria (9). Fatty acids are usually potent inhibitors of oxidation and phosphorylation (unpublished observations). By means of incorporating carboxyl $C^{14}$-labeled palmitate into the endogenous lipids, rat-brain homogenates were shown to oxidize lipids in the presence or absence of glucose at a rate comparable to that of liver (11). During glucose-free perfusion of cat brain, considerable amounts of phospholipids were found to disappear from the cerebral cortex, and it was not possible to account for them on the basis of lipids leaving the brain (3). In the light of these positive findings, the repeated failures to demonstratd fatty acid oxidation in preparations of neural tissue is puzzling. It is conceivable that the tissue damage occurring in *in vitro* preparations may be sufficient to either release inhibitory factors (perhaps the lipids themselves) or greatly

inactivate the fatty acid oxidase system. The problem of fatty acid metabolism in neural tissue is unquestionably an important one and offers a challenge for physiologists and biochemists alike.

The problem with regard to phospholipid metabolism is more promising but considerably more complex. When brain homogenates are actively incorporating orthophosphate-$P^{32}$ into lipids, phosphatidylethanolamine, phosphatidylserine and sphingomyelin show only a slight incorporation of $P^{32}$, whereas diphosphoinositide has a specific activity comparable to ATP and other acid-soluble phosphates (23). Lecithin showed a low, yet significant turnover. Peripheral nerve respiring in glucose will incorporate orthophosphate-$P^{32}$ into phospholipids, and at a considerably greater rate during nerve degeneration (81). The metabolically active lipids are presumably in the Schwann cell, the myelin lipids being relatively inert. Myelin formation and, therefore, a significant fraction of phospholipid synthesis in the central nervous system have been attributed to certain neuroglia (73). In the peripheral nervous system the Schwann cells, which are embryologically similar to oligodendroglia, seem definitely to be involved in myelin formation (47).

Phospholipid synthesis involves a specific coenzyme, cytidine diphosphate, which in the presence of phosphotransferases will react with choline or ethanolamine to form CDP-choline or CDP-ethanolamine (66, 67). The next enzymatic step involves the conversion of the cytidyl compounds to lecithin and phosphatidylethanolamine. This enzymatic system is widely distributed in nature and is present in cat brain (Kennedy, E. P., personal communication).

### NUCLEIC ACIDS

By means of elegant biophysical and cytochemical techniques, Hydén and collaborators have made extensive studies on the nucleoprotein content and distribution of various nerve cells under conditions of rest and activity. After intense muscular exercise both the RNA and protein content of the anterior horn cells decrease to less than one third the original amount, while the ganglion cells associated with the eighth nerve show a significant increase in RNA during the 1st hr. of electrical stimulation and a considerable decrease with the onset of fatigue during prolonged stimulation (49). The necessity of normal stimulation for adequate development of retinal ganglion cells is made apparent from the observation that the RNA and protein content showed the normal increase only if the animal received normal light stimulation (16). Under a variety of conditions resulting in a loss of function, the RNA content of neurons is rapidly depleted. [This topic has been reviewed by Hydén (62).]

A marked depletion of the cytoplasmic RNA in the supraoptic nuclei of the hypothalamus occurred as a result of fasting for 24 hr., while the cytoplasmic protein content appeared to increase (89). If rats are subjected to a brief period of cold, the cytoplasmic RNA of the supraoptic nuclei increases significantly; but after exposure to cold for 1 hr., a precipitous decrease in the RNA occurs.

Since the role of RNA and DNA in the cell is closely linked with protein synthesis, changes in their cellular content would be expected to correlate with the appearance of enzymes. In the embryonic stage of the nervous system when the neuron begins to mature and numerous respiratory enzymes appear, the content of RNA and DNA is extremely high. As the respiratory enzymes reach a nearly maximal rate, just before birth, the RNA has decreased one third, while the DNA has fallen to less than one half its initial value (90). After birth the nucleic acid content of the central nervous system remains fairly constant. Both the activity of ribonuclease and desoxyribonuclease, as well as the phosphate turnover of the nucleic acids, are correlated with the rate of disappearance of the nucleic acids (60). There appears to be a relationship between the density of RNA and the degree of neuronal differentiation in the embryonic nervous system (61).

### RELATIONSHIP OF CHEMISTRY TO FUNCTION

Even a brief survey of the historical development of the chemistry of neural tissue reveals that the problem has been consistently dealt with in terms of its function; and although such attempts have been largely inconclusive, owing to the difficulty of techniques, important groundwork has been laid for future developments.

Ever since the hypothesis was proposed that muscle contraction involved the splitting of ATP and was consequently an endergonic process, the tendency to regard nerve conduction in the same way has been prevalent, and almost categorical. The evidence that respiratory metabolism increased during activity in neural tissue is overwhelming (25, 29), and the increased production of heat during nerve conduction

was discovered a quarter of a century ago (42). Depolarization of conductive tissue was believed to be metabolically passive, involving pre-existing electrochemical gradients, while repolarization was a process requiring energy. The source of energy was thought to be largely from carbohydrate metabolism via ATP, but there was evidence that noncarbohydrate substrates were involved, particularly during activity (39, 42, 44). With the advent of the theory that nerve conduction was directly related to the transport of sodium and potassium (55), interest was renewed in the problem of selective ionic accumulation and the metabolic factors accompanying it. Excitability of conductive tissue is dependent upon the ability to maintain a high internal potassium concentration against a strong electrochemical gradient. Metabolic energy was presumed to be necessary for maintaining potassium influx as well as the efflux of the sodium entering during activity (55).

In studies with the giant axon of *Sepia loligo* it has been found that metabolic inhibitors such as cyanide, azide and dinitrophenol, as well as cooling to 1 °C, will block both sodium extrusion and potassium uptake in the resting state, while dinitrophenol had only a slight effect on the rapid movements of sodium during the passage of impulses (56). Hodgkin & Keynes (56) concluded from such observations that the 'permeability system,' which allows ionic transport across an electrochemical gradient during activity, is not metabolically dependent as is the 'secretory mechanism' which is operative only during the recovery phase. The movement of ions during activity, which is some 2,000 times greater than is possible at rest (56), is a process requiring only an increase in permeability allowing sodium and potassium to move down electrochemical gradients.

Another mechanism for the action potential attributes the net influx of sodium to a transient inhibition of the metabolic process extruding sodium (48). Such a view is consistent with the observation that the major pathway of energy production is inhibited during excitation in nerve fibers (8, 9). The increase in respiratory activity occurring during excitation is not coupled to increased phosphorylation, so that a true 'uncoupling' of oxidation and phosphorylation may be taking place (8). Such a mechanism for sodium entry during activity would obviate the difficulties incumbent in the concept of 'membrane permeability' (76). There is evidence from many sources to indicate that excitation is accompanied by decreased energy output; in brain slices (82, 83), brain mitochondria (9) and sartorius muscle (64, 111), the uptake of orthophosphate-$P^{32}$ by frog nerves is inhibited during excitation (8). A considerable decrease in the K Na ratio, and in $K^{42}$ turnover of rat brain and muscle mitochondria has been observed with electrical excitation as well as dinitrophenol (5). These observations, along with the finding that a depletion of intramitochondrial potassium results in decreased phosphorylation support the thesis that K-Na transport and phosphorylation are closely related (8, 56).

Inhibition of synthetic reactions during increased activity may also be the mechanism whereby ATP is rapidly degraded. It does not appear unlikely that catabolic reactions are generally held in check by anabolic ones, and only after the latter are suppressed will the former become accelerated. The maintenance of intracellular K in brain slices and retina is dependent, not only on phosphorylation, or an energy source, but also upon the presence of glutamic acid (112). It is not at all clear what the role of glutamic acid is in nerve function, although it is involved in a diverse number of interesting chemical reactions. Besides being a source of metabolic energy, glutamate is also involved in the depletion of ATP according to the following reaction:

$$\text{glutamate} + \text{ATP} + \text{NH}_3 \leftrightharpoons \text{glutamine} + \text{ADP} + \text{P}$$

This reaction may be of importance in the removal of the highly toxic ammonia formed as a result of activity (96). Recently, γ-aminobutyric acid formed by the decarboxylation of glutamate has been shown to have an inhibitory effect (anticholinergic) on neural activity and may be acting as a neurohumoral agent (26, 51). Of particular significance is the fact that glutamic acid decarboxylase increases rather abruptly during the period of neuronal maturation (97). Another possible function of intracellular glutamic acid is in the regulation of the relative amounts of free and bound acetylcholine (114). The diverse functional roles of glutamate and its derivatives are highly suggestive of its importance in neural function, although the precise links and mechanisms have yet to be elucidated.

In connection with the problem of phosphorylation during activity, there are two points to discuss; one concerned with a possible mechanism by which electrical currents can alter phosphorylation, and the other with the problem of whether excitability is a process directly dependent on energy production or an active process of sodium extrusion. One explanation for the mechanism by which electrical

currents can affect metabolism is by means of ionophoresis in such a manner as to alter the effective concentration of an essential ion at an enzyme surface (9). A depletion of intramitochondrial potassium during excitation may be sufficient to bring about an inhibition of phosphorylation or, perhaps, a critical displacement of other ions essential to phosphorylation, such as magnesium or DPN. Another possibility is that excitation induces certain reversible structural alterations within the mitochondria which are sufficient to disturb the delicate balance of organization essential to phosphorylation (8, 9). The work of Tobias and others (19, 113) and Hill (52) leaves little doubt that significant structural changes are concomitant with nerve conduction; and since these changes seem to involve particulates, it is not inconceivable that mitochondrial metabolism is altered.

Recently, extremely interesting changes have been observed in neurons cultured *in vitro* under the influence of neurotropic drugs and during electrical stimulation (41; personal communication). Electrical excitation and pentylenetetrazol caused the nucleus to appear enlarged while accelerating movements of the cytoplasmic granules and nucleolus. In addition, the neuronal processes become more motile, may shorten and become beaded with large clumps of granules. Depressant drugs, on the other hand, result in an almost complete disappearance of cytoplasmic granules, with complete reappearance in 15 min. Whether or not the granules actually disappear and are resynthesized *de novo* is not certain, but the conclusion is inescapable that mitochondria and other granules are responsive to variations in neuronal activity.

There is still another point to discuss in regard to the failure to observe increased phosphorylation during excitation, namely, the possibility that forms of 'high energy' bonds other than phosphates may be exhibiting an increased turnover. An exergonic reaction of considerable magnitude is that involving transacetylation of thiol esters such as in the following reaction:

$$\text{AMP} + \text{acyl-Co AS} + \text{PP} \rightleftarrows \text{ATP} + \text{CoA SH} + \text{acyl compound}$$

The hydrolysis of acyl imidazoles is also an exergonic reaction (109, 116),

$$\text{acetyl-CoA} + \text{imidazole} \rightleftarrows \text{acetyl-imidazole} + \text{CoA}$$

$$\text{acetyl-Im} + \text{P} \rightleftarrows \text{acetyl-P} + \text{imidazole}$$

Although attempts to demonstrate the enzymatic acetylation of histidine, carnosine and other biochemically important imidazoles have been so far unsuccessful, the possibility that such reactions do occur certainly exists.

The intracellular accumulation of cations has been attributed to a diverse number of cellular components, including various structural components. In an effort to account for the intracellular accumulation of potassium and sodium on the basis of soluble anions, such as amino acids and phosphates, a sulphydryl compound, isothionic, was discovered in squid axoplasm which presumably made up this 'anion deficit' (70). The 'fixed-charge hypothesis' of Ling (76) has endeavored to explain the selective accumulation of potassium on the basis that the smaller hydrated potassium ion has a greater adsorption energy than sodium and is, thereby, more likely to combine with 'fixed charges.' Although protein molecules in the alkaline range have many free anionic sites, many other structural components, such as nucleic acids, phosphatides and even mucopolysaccharides could be involved (cf. 1). In addition to possessing available anionic sites, many of these components are polymers capable of altering their structural configuration and thereby the availability of binding sites. The degree of cross linkages in polystyrene resins, for example, greatly influences the selective binding of potassium (76). Ion transport during excitatory activity may be accompanied by reversible alterations in the polymeric configuration of such substances (1).

As is evident from the foregoing discussion, as well as from the history of the chemistry of muscle contraction, the question of function is inextricably linked to the chemical events of the neuron. If the fundamental event in nerve conduction should prove to be explainable on the basis of the sodium-potassium flux concept, future effort should be directed towards an elucidation of the metabolic and physicochemical events regulating ion exchange. Such concepts as ion binding, permeability and active transport are strictly dynamic ones involving a complex of chemical processes all the way from energetic transformation to the intramolecular rearrangements within proteins and other polymeric substances within the cell. The study of the neuron demands an intermingling of all the available techniques of the natural sciences, and any severe compartmentalization of disciplines would be particularly misleading with regard to the neuron.

Neuronal chemistry, at least as far as concerns our

knowledge to date, does not differ greatly from the chemistry of other tissues; therefore, it would seem more probable that its peculiarity is attributable to the particular relations it has to the unique structural and functional organization of the neuron. It is extremely fortunate that such a multidisciplinary approach is becoming increasingly more prevalent in the field of the nervous system. The past decade has witnessed a tremendous surge in our knowledge of neuronal chemistry, and within the next quarter century its relation to the excitatory events themselves should become considerably more clear.

## REFERENCES


1. Abood, L. G. and S. K. Abul-Haj. *J. Neurochem.* 1: 119, 1956.
2. Abood, L. G., M. Cavanaugh, R. D. Tschirgi and R. W. Gerard. *Fed. Proc.* 10: 3, 1951.
3. Abood, L. G. and A. E. Geiger. *Am. J. Physiol.* 182: 557, 1955.
4. Abood, L. G. and R. W. Gerard. *Am. J. Physiol.* 168: 739, 1952.
5. Abood, L. G. and R. W. Gerard. *Am. J. Physiol.* 179: 613, 1954.
6. Abood, L. G. and R. W. Gerard. *J. Cell. & Comp. Physiol.* 43: 379, 1954.
7. Abood, L. G., R. W. Gerard, J. Banks and R. D. Tschirgi. *Am. J. Physiol.* 168: 729, 1952.
8. Abood, L. G. and E. Goldman. *Am. J. Physiol.* 184: 329, 1956.
9. Abood, L. G. and L. Romanchek. *Biochem. J.* 60: 233, 1955.
10. Abood, L. G. and L. Romanchek. *Exper. Cell Res.* 8: 459, 1955.
11. Allen, A., B. Friedmann and S. Weinhouse. *J. Biol. Chem.* 212: 921, 1955.
12. Bear, R. S., F. O. Schmitt and J. Z. Young. *Proc. Roy. Soc., London. ser. B* 123: 505, 1937.
13. Bodian, D. In: *The Nerve Impulse*, edited by D. Nachmansohn. New York: Macy, 1951, vol. I, p. 108.
14. Boeke, J. In: *Genetic Neurology*, edited by P. Weiss. Chicago: Univ. Chicago Press, 1950, p. 78.
15. Brante, G. *Acta physiol. scandinav.* 18: Suppl. 63, 1949.
16. Brattgård, S. O. *Acta radiol.* Suppl. 96, 1952.
17. Brattgård, S. and H. Hydén. *Acta radiol.* Suppl. 94, 1952.
18. Brody, T. and J. A. Bain. *J. Biol. Chem.* 195: 685, 1952.
19. Bryant, S. H. and J. M. Tobias. *J. Cell. & Comp. Physiol.* 46: 71, 1955.
20. Cohen, S., R. Levi-Montalcini and V. Hamburger. *Proc. Amer. Ass. Cancer Res.* 1: 9, 1954.
21. Copenhaver, J. H., Jr., M. E. Nagler and A. Goth. *J. Pharmacol. & Exper. Therap.* 109: 401, 1953.
22. Davies, D. R. and L. G. Thomas. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 170.
23. Dawson, R. M. C. *Biochem. J.* 57: 237, 1954.
24. De Robertis, E. D. P. and H. S. Bennett. In: *Fine Structure of Cells*. New York: Interscience, 1955, p. 261.
25. Doty, R. W. and R. W. Gerard. *Am. J. Physiol.* 162: 458, 1950.
26. Elliott, K. A. C. and E. Florey. *XX Internat. Physiol. Congr., Abstr. of Communic.* 268, 1956.
27. Elliott, K. A. C., I. H. Page and J. H. Quastel (editors). *Neurochemistry*. Springfield: Thomas, 1955.
28. Engström, A. *Progr. Biophys. and Biophys. Chem.* 1: 164, 1950.
29. Enström, A. and B. Lindstrom. *Biochim. et biophys. acta* 4: 351, 1950.
30. Fatt, P. and B. Katz. *J. Physiol.* 115: 320, 1951.
31. Finean, J. B. *Exper. Cell Res.* 5: 202, 1953.
32. Finean, J. B. *Experientia* 9: 17, 1953.
33. Folch, J. In: *Phosphorus Metabolism*, edited by W. D. McElroy and B. Glass. Baltimore: Johns Hopkins Press, 1952, p. 186.
34. Folch-Pi, J. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 121.
35. Fox, D. L. *Animal Biochromes and Structural Colours*. New York: Cambridge, 1953.
36. Gartonde, M. K. and D. Richter. *Biochem. J.* 59: 690, 1955.
37. Gasser, H. S. *Sympos. Quant. Biol.* XVII: 34, 1952.
38. Geiger, A., J. Magnes and R. Geiger. *Nature, London* 170: 754, 1952.
39. Geiger, A., S. Yamasaki and R. Lyons. *Am. J. Physiol.* 184: 239, 1956.
40. Geiger, R. S. *A. M. A. Arch. Neurol. & Psychiat.* 75: 442, 1956.
40a. Geiger, R. S. *Exper. Cell Res.* 14: 541, 1958.
41. Geiger, R. S. *Fed. Proc.* 15: 71, 1956.
42. Gerard, R. W. *Physiol. Rev.* 12: 469, 1932.
43. Gerard, R. W. In: *Genetic Neurology*, edited by P. Weiss. Chicago: Univ. Chicago Press, 1950.
44. Gerard, R. W. and N. Tupikova. *J. Comp. & Cell. Physiol.* 13: 1, 1939.
45. Gerebtzoff, M. A. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 315.
46. Geren, B. B. *Exper. Cell Res.* 7: 558, 1954.
47. Geren, B. B. and F. O. Schmitt. In: *Fine Structure of Cells*. New York: Interscience, 1955, p. 251.
48. Grundfest, H. *Progr. Neurol. and Psychiat.* 5: 16, 1950.
49. Hamberger, C. A. and H. Hydén. *Acta oto-laryng.* Suppl. 65: 53, 1949.
50. Havet, J. *Trab. Lab. Invest. Biol. Univ. Madrid* 14: 35, 1916.
51. Hayashi, T. and K. Nagai. *Internat. Physiol. Congr., Abstr. of Communic.* 410, 1956.
52. Hill, D. K. and R. D. Keynes. *J. Physiol.* 108: 278, 1949.
53. Hillarp, N. A. and B. Nelson. *Acta physiol. scandinav.* 32: 11, 1954.
54. Himwich, H. A. and M. H. Aprison. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 301.

55. Hodgkin, A. L., A. Huxley and B. Katz. *J. Physiol.* 116: 424, 1952.
56. Hodgkin, A. L. and R. D. Keynes. *J. Physiol.* 128: 28, 1955.
57. Hoffman, H. *Australian J. Exper. Biol. & M. Sc.* 30: 541, 1952.
58. Hollinger, D. M. and R. J. Rossiter. *Biochem. J.* 52: 659, 1952.
59. Hollinger, D. M., R. J. Rossiter and H. Upinalis. *Biochem. J.* 52: 652, 1952.
60. Hughes, A. F. W. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 166.
61. Hydén, H. *Acta physiol. scandinav.* 6: Suppl. 17, 1943.
62. Hydén, H. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955, p. 204.
63. *IV Internat. Congr. Biochem., Proc.* New York: Pergamon, 1959, vol. III.
64. Janke, J. *XV Internat. Physiol. Congr., Abstr. of Communic.* 470, 1956.
65. Johnson, A. C., A. R. McNabb and R. J. Rossiter. *Biochem. J.* 43: 573, 1948.
66. Kennedy, E. P. and S. B. Weiss. *J. Am. Chem. Soc.* 77: 250, 1955.
67. Kennedy, E. P. and S. B. Weiss. *J. Biol. Chem.* 222: 193, 1956.
68. Klenk, E. and H. Langerbeins. *Ztschr. physiol. Chem.* 270: 185, 1951.
69. Klüver, H. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 137.
70. Koechlin, A. *Fed. Proc.* 13: 80, 1954.
71. Koelle, G. B. *J. Comp. Neurol.* 100: 211, 1954.
72. Kollross, J. J., V. Perpernick, B. Hill and J. C. Kaltenbach. *Anat. Rec.* 108: 565, 1950.
73. Korey, S. R. *Fed. Proc.* 14: 238, 1955.
74. Levi-Montalcini, R. and V. Hamburger. *J. Exper. Zool.* 123: 233, 1953.
75. Lewis, P. R. *Biochem. J.* 52: 330, 1952.
76. Ling, G. In: *Phosphorus Metabolism*, edited by W. D. McElroy and B. Glass. Baltimore: Johns Hopkins Press, 1952, vol. II, p. 748.
77. Logan, J. E., W. A. Mannell and R. J. Rossiter. *Biochem. J.* 51: 482, 1952.
78. Lowry, O. H., N. R. Roberts and M. W. Chang. *J. Biol. Chem.* 222: 97, 1956.
79. Lowry, O. H., N. R. Roberts, K. Y. Leiner, M. Wu, L. Farr and R. W. Albers. *J. Biol. Chem.* 207: 39, 1954.
80. Lowry, O. H., N. R. Roberts and C. Lewis. *J. Biol. Chem.* 220: 879, 1956.
81. Magee, W. L. and R. J. Rossiter. *Biochem. J.* 58: 243, 1954.
82. McIlwain, H. *Biochem. J.* 49: 382, 1951.
83. McIlwain, H., L. Buchel and J. D Cheshire. *Biochem. J.* 48: 12, 1951.
84. Monné, L. *Advances in Enzymol.* 8: 1, 1948.
85. Monné, L. *Arch. exper. Zellforsch. Gewebezücht.* 23: 157, 1939.
86. Mullins, L. J. *Am. J. Physiol.* 175: 358, 1953.
87. Nageotte, J. *Compt. rend. Soc. de biol.* 68: 1068, 1910.
88. Naido, D. and O. E. Pratt. *J. Neurol. Neurosurg. & Psychiat.* 14: 287, 1951.
89. Nurnberger, J. I. *A. Res. Nerv. & Ment. Dis., Proc.* 32: 132, 1953.
90. Palladin, A. V. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 177.
91. Parker, M. W., S. B. Hendricks, H. A. Borthwick and C. E. Jenner. *Nature, London* 169: 242, 1952.
92. Pope, A. *J. Neurophysiol.* 15: 115, 1952.
93. Pope, A., H. H. Hess, J. R. Ware and R. H. Thomson. *J. Neurophysiol.* 19: 259, 1956.
94. Ramón y Cajal, S. *Degeneration and Regeneration of the Nervous System.* London: Oxford, 1928.
95. Richter, D. (editor). *Metabolism of the Nervous System.* New York: Pergamon, 1957.
96. Richter, D. and R. M. C. Dawson. *J. Biol. Chem.* 176: 1199, 1948.
97. Roberts, E. In: *Neurochemistry*, edited by S. R. Korey and J. I. Nurnberger. New York: Hoeber, 1956, p. 11.
98. Robins, E., K. M. Eydt and D. E. Smith. *J. Biol. Chem.* 220: 677, 1956.
99. Robins, E., D. E. Smith and K. M. Eydt. *J. Neurochem.* 1: 54, 1956.
100. Robins, E., D. E. Smith, K. M. Eydt and R. E. McCaman. *J. Neurochem.* 1: 68, 1956.
101. Robins, E., D. E. Smith and V. R. E. McCaman. *J. Biol. Chem.* 204: 927, 1955.
102. Runnström, J. *Exper. Cell Res.* 9: 241, 1949.
103. Scharrer, B. C. *J. Comp. Neurol.* 70: 77, 1939.
104. Schmitt, F. O., R. S. Bear and K. Palmer. *J. Cell. & Comp. Physiol.* 18: 31, 1941.
105. Schuwirth, K. *Ztschr. physiol. Chem.* 263: 25, 1940.
106. Shepherd, J. A. and G. Kalnitsky. *J. Biol. Chem.* 207: 605, 1954.
107. Sjostrand, F. S. *J. Cell. & Comp. Physiol.* 42: 45, 1953.
108. Snyder, J., L. G. Abood and R. W. Gerard. *Fed. Proc.* 11: 151, 1952.
109. Stadtman, E. R. In: *Mechanism of Enzyme Action*, edited by W. D. McElroy and B. Glass. Baltimore: Johns Hopkins Press, 1954, p. 581.
110. Strominger, J. L. and O. H. Lowry. *J. Biol. Chem.* 213: 635, 1955.
111. Taylor, R. E. and L. G. Abood. *Am. J. Physiol.* 171: 772, 1952.
112. Terner, C., L. V. Eggleston and H. A. Krebs. *Biochem. J.* 47: 139, 1951.
113. Tobias, J. M. and S. Solomon. *J. Cell. & Comp. Physiol.* 35: 25, 1949.
114. Tower, D. B. *Neurology* 113: 5, 1955.
115. von Economo, C. *Zellaufbau der Grosshirnrinde des Menschen.* Berlin: Springer, 1927.
116. Vrba, R. *J. Neurochem.* 1: 12, 1956.
117. Waelsch, H. *Advances in Enzymol.* 13: 237, 1952.
118. Waelsch, H. (editor). *Biochemistry of the Developing Nervous System.* New York: Acad. Press, 1955.
119. Weiss, P. and H. B. Hiscoe. *J. Exper. Zool.* 107: 315, 1948.
120. Wislocki, G. B. and R. L. Sidman. *J. Comp. Neurol.* 101: 53, 1954.
121. Wooley, D. W. and E. Shaw. *Ann. New York Acad. Sc.* 66: 649, 1957.

CHAPTER LXXVI

# Central nervous system metabolism in vitro

P. J. HEALD
H. McILWAIN
G. H. SLOANE-STANLEY

*Institute of Psychiatry (British Postgraduate Medical Federation, University of London), Maudsley Hospital, London, England*

CHAPTER CONTENTS



THIS SECTION covers, in summary fashion, metabolic studies in systems of the following distinct types: *a*) the intact central nervous system which has been the subject of only a few successful metabolic *in vitro* studies; *b*) sections from the central nervous system largely retaining cell structure which have been very extensively studies; *c*) systems in which cell structure has been destroyed but which nevertheless contain all the material of the whole tissue, unfractionated; *d*) particulate or other preparations in which organized metabolic cycles or sequences occur; and *e*) preparations, usually cell-free and fractionated, in which individual enzymes can be examined.

In these different systems it is usual for the technique of study, and also the problems which can usefully be studied, to differ considerably. Broadly speaking, in systems *a* and *b* the metabolic events which can be examined approximate fairly closely those accessible *in vivo*. At *c* a major transformation occurs in the control of metabolism, the type of substrate accessible to tissue enzymes and the functional potentialities of the preparation. In systems *d* and *e*, only relatively isolated aspects of metabolism are open to study; for example, energy-yielding and energy-consuming processes are separated, and the studies tend to have as their objective an analysis or understanding of events *in vivo* rather than their simulation.

Specific references are often not given to work which has already been documented and appraised (136); the collected papers (43, 97) may also be consulted.

## TECHNIQUES

### *Preparation of Tissue*

A major factor in making satisfactory cell-containing tissue preparations is that materials, which *in vivo* reach the central nervous system from blood capillaries, should be adequately replaced by materials arriving either from perfusion fluids or by diffusion from an outer surface of the isolated tissue. In the

absence of an adequate supply of materials, cell integrity fails and, with such failure, metabolic and other characteristics which depend on cell structure also change. The totality of substances which must be supplied to these tissues to maintain them chemically and otherwise similar to their *in vivo* condition is not yet known; approximations which have proved adequate for many studies are described in the following section. The two substances which are most important are oxygen and glucose; of these, oxygen is the substance which by its diffusion brings defined physical limits to the size of the preparation which can be studied. Calculation and experiment indicate that with a tissue of respiratory rate of some 100 $\mu$mole $O_2$ per gm fresh wt. per hr., such as cerebral cortex, diffusion of oxygen from a solution in equilibrium with an atmosphere of 100 per cent $O_2$ gives adequate oxygenation to a depth of about 0.15 to 0.2 mm. Accepting this limitation, the tissue can therefore be prepared with minimal damage in the form of a sheet 0.3 to 0.4 mm in thickness. Corresponding thickness for white matter of respiratory rate 25 or 50 $\mu$mole $O_2$ per gm per hr. would be about 0.5 to 0.7 mm. It will be noted that these arrangements, which are the ones most frequently adopted, expose the outer parts of the tissue to unusually high oxygen tensions while in the center of the slice tension may be lower than *in vivo*. Methods for slicing the tissue to this form have been described (125, 190).

From small or irregularly shaped pieces of tissue, slices are best prepared by chopping (139). A mechanical chopper has been devised which enables blocks of white matter, otherwise difficult to slice, to be uniformly chopped.[1] From most parts of the central nervous system, cell-containing suspensions which can be pipetted may be obtained by chopping twice in two directions at right angles to each other. The mechanical chopper enables the transition from cell-containing to cell-free systems to be appraised. When cuts are made at intervals of 0.02 mm in two directions at right angles to each other, systems intermediate in properties between the normal slice and homogenate are obtained. Intermediate preparations may also be obtained by enzymic treatment of the cell-containing tissue, yielding from cerebral cortex an approximation to a cell-suspension (132).

Systems in which cell structure has been destroyed are normally prepared by grinding tissues in aqueous fluids; other procedures are noted subsequently. Grinding in water or in greatly hypotonic solutions disturbs not only cell structure but also subcellular elements and is to be regarded as a possible preliminary to systems containing individual enzymes rather than to those now under consideration. These typically employ dispersion in approximately isotonic or hyptertonic solutions at 0–4°C. Most use (1, 22, 59, 79, 158, 183) has been made of 0.25 M sucrose following procedures developed primarily in connection with tissues other than those of the central nervous system. In first using a given homogenizer for a given tissue, an investigator must examine microscopically the resulting suspension or preparations from it in order to choose grinding conditions which do in fact give minimal residual cell structure. The breakdown is of course gradual, and with brief grinding or a loosely fitting pestle even large cells will remain intact, shorn of the greater part of their axons and dendrites.

Many studies have employed unfractionated homogenates; in others, separation into three or four fractions has been carried out by centrifuging, most frequently in the sucrose in which the tissue was ground (22, 23, 161). Chemical and enzymic analyses of the fractions have been made (2, 22, 59). As in other tissues, the fractions recognized have been predominantly unchanged cells, nuclei, mitochondria, microsomes and soluble components. Probably more consideration should be given to the fate of the myelin, to subcellular entities other than those named and to selection of discrete parts of the central nervous system before homogenizing. Separation of secretory granules from the pituitary gives a valuable example (228).

Preparation of tissues for histochemical study can often be regarded from a metabolic point of view as yielding systems of the *c* type, for although relative positions of subcellular entities in the cell may be preserved, selective permeability of the cell is usually not. Freeze-drying and sectioning methods have been developed (118, 119, 155, 156, 200) specifically for displaying chemical and metabolic attributes of central nervous tissues. In these methods the tissue may be frozen, sectioned, dehydrated while frozen and microdissected while dry (118, 119) or while in oils (38); or frozen, dried, embedded in paraffin, sectioned and extracted with a fat solvent (156). Cognate procedures, on a preparative scale, have been to freeze-dry blocks of tissue, grind these in nonaqueous solvents, and separate therefrom nuclei and other subcellular particles.

For study of specific enzyme systems, a few illustrative examples, specific to central nervous tissues, may

[1] H. Mickle Mill Works, Gomshall, Surrey, England.

be quoted. The tissues may be prepared by extraction with water (124, 221) and subsequent dialysis (226) and by extraction with salts and buffers (105, 212). Extraction has frequently been carried out in aqueous solutions after an initial acetone-drying of the tissue (71, 148, 187, 195); extraction fluids have in some cases included cysteine (71, 78, 187) and the acetone drying has been carried out with the frozen tissue (152). In such extracts, metabolic potentialities may for the purpose of study be limited to one or a few enzyme reactions by supplying a specific substrate (148, 149, 176), by the use of inhibitors (154) or by the use of activators (176). The purification of individual enzymes is beyond the scope of the present review.

*Metabolic Conditions*

For preparations with intact cells, metabolites, including oxygen which has already received comment, are normally provided in an aqueous medium which contains also salts, buffers and organic substrates. The medium may be a modified or simplified blood (60), physiological salt solution (35, 103, 177) or various enriched salines (103, 146, 206, 207).

There is no one metabolic criterion of the adequacy of metabolic conditions; these must be appraised in relation to the object of the *in vitro* study. A minimum requirement can usually be stated, namely, that the main energy-yielding requirements of the tissue should be met. This is best judged by the maintenance of energy-rich phosphates in the tissue, or by the ability of the tissue to show metabolic response to electrical pulses (see below); respiration gives a much less certain criterion. Parallel to such maintenance go other activities of the tissue such as the incorporation of isotopes into structural materials (47). This minimum is provided by a salt mixture plus oxygen and glucose. Glucose, with white matter (17) as well as with gray, with subcortical (17) as well as with cortical tissues, and with human (130) as well as with other central nervous system tissues, is usually replaceable by pyruvate but not by lactate, citrate, succinate or fumarate. A high concentration of fructose may replace glucose, and glutamate is more effective with human tissues than with tissues from other species.

The minimal conditions give tissues known to be depleted with respect to many of their organic constituents and of respiratory rate lower than *in vivo*. Several specific additions to the minimal saline make good some of the deficiencies; detailed study has been made of glutamate and potassium salts (104, 191), chlorides (208), creatine (206), adenosine and guanosine derivatives (76, 207), glycogen (109, 147), glutathione (144), glucose and lactate (147). When any of these or related substances are added to salines containing central nervous tissues, incubation for appreciable times may be necessary for restoring *in vivo* composition or an approximation to it. Several deficiencies are made good in a few minutes but others such as glycogen and nucleotides may require 2 hr. at 37°C.

The deficiencies already described arise spontaneously as a result of removing tissues from animals and placing them in many times their volume of simple salines. More may be learned about chemical requirements for tissue functioning by deliberately inducing further depletion in the tissue by incubating it without glucose (142) or without oxygen (135). Conversely, the depletion may be minimized by incubating the tissue with only very small volumes of salines (177) or in oils (177); experimental arrangements have been described for supplying substrates and for electrically stimulating cerebral tissues under these conditions.

In the case of preparations not maintaining cell structure, choice of metabolic conditions should imitate intracellular rather than extracellular fluids. Again, however, conditions must be appraised in relation to the specific objective of the study and may differ greatly. Regarding individual cerebral enzymes, systems are too diverse to receive general comment; many individual examples have been quoted (136). As many processes require maintenance of the main energy-yielding reactions of the tissue, requirements for these may be noted. For glycolysis in cell-free systems conditions are well documented (43, 136); they involve several intermediary metabolites and coenzymes and also some additions not native to the tissue as, for example, high concentrations of nicotinamide to prevent loss of cozymase (145). Requirements of oxidative phosphorylation (22, 25, 27) include supplementing the tissue's store of phosphate acceptors with added adenosine mono- or diphosphate, or glucose plus hexokinase. When first studied in mitochondrial preparations, oxidatively phosphorylating systems proved labile so that experiments were often run below 37°C and for periods of only 5 to 30 min. More stable preparations have subsequently become available (27) which allow, with an agent such as ethylenediamine tetra-acetic acid, much longer experimental periods. The tetra-acetic acid may act in part by chelating traces of toxic metals, to which cell-free systems are in general much more susceptible (26, 134) than are cell-containing

systems. Probably other organized enzyme sequences will prove to have requirements as defined as those for the well-investigated energy-yielding reactions, but data are as yet incomplete.

*Metabolic Response to Electrical Excitation*

Metabolic changes in response to applied electrical pulses have been observed *in vitro* in the whole brain from lower vertebrates and in cell-containing preparations from all parts of the mammalian central nervous system which have been so examined (17, 19, 134, 136). There have been described suitable sources of electrical pulses (10, 125), electrodes for their application (10, 126), and precautions and control experiments employed in interpreting results (125, 135, 158).

Techniques fall into two main categories. First are those in which response is judged by measurement of changes in the tissue environment, the consumption of substrates or formation of products. The second comprises those in which the tissue itself is analyzed. In the first category, much use has been made of orthodox manometric techniques for measuring oxygen consumption (125, 136) or, in bicarbonate salines, for measuring acid formation (137). With cerebral cortex almost all the acid formed from glucose is lactic acid (137, 143). These procedures have the virtue of enabling, with a single sample of tissue, measurement during successive periods in which the tissue is first unstimulated, then receives electrical pulses and then is again unstimulated. Pulses may be passed for some 2 hr. without adversely affecting the tissue; in ordinary apparatus, 15 to 40 min. suffice for accurate manometric measurements. More rapid potentiometric methods for determing the oxygen consumption of stimulated tissues have been devised and applied to ganglia (106). In the second category, the means often used for handling tissues for subsequent analysis are little different from those described above (140); it is only necessary to note that for measurement of labile substances, fixation must follow promptly after cessation of pulses. For this purpose special apparatus has been devised and is described in the following section.

By whatever means response is measured, it is found that in order to obtain maximal response from a tissue such as the mammalian cerebral cortex, almost the whole of the tissue sample must be within an appreciable potential gradient. Two main types of electrodes have been employed to give the necessary gradient. In one, the electrodes are at the center and periphery of the annular space of a conical manometric vessel (10, 126). They thus encompass almost the whole of a shallow layer of fluid in which fragments of tissue of 0.1 to 10 mg are floating freely. This is the arrangement most appropriate when small and irregularly shaped tissue fragments are to be examined. It is also applicable to the cell-containing, chopped-tissue suspensions described in a previous section, but is not suitable if the tissue is to be collected rapidly for analysis. A fixing agent may however be tipped from a side arm during the passage of pulses. In the second arrangement, the tissue as a sheet some 1 x 1.5 cm in size lies between grids of wires which alternately are of opposite polarity when pulses are applied. This is the arrangement most appropriate when the tissue is to be analyzed at the end of an experiment, or when the spread of excitation from the electrodes is under investigation.

Characteristics of electrical pulses required for excitation are similar in the two experimental arrangements when the potentials applied are expressed as peak potential gradients (133, 134). Neither type of electrode gives a uniform potential gradient; gradients with the present types have been recorded (10, 77). Maximal metabolic responses are typically obtained when pulses of exponential time-voltage relationship and peak potential gradient of 1 v. per mm with a time-constant of 0.3 msec. are applied at 100 per sec. by use of which response-voltage curves and other relationships have been worked out (67, 133). Metabolic response is given also to sine waves but requires expenditure in the fluid of much more electrical energy, and to bursts of pulses with relatively long (1 sec.) intervals (114, 133, 227).

*Metabolic Studies in Brief Experimental Periods*

The rapid action of the central nervous system *in vivo* is paralleled by the rapidity of change in its metabolic activity. Study of comparable phenomena *in vitro* involves three operations: *a*) preparing tissues and re-establishing defined levels in the chemical or metabolic characteristics under investigation which may require, according to the substances or processes concerned, a few minutes, or an hour or more; *b*) rapidly inducing a changed level of activity; and *c*) rapid analysis or fixation.

Of analytical methods, potentiometric means of measuring respiration have already been noted. The methods of fixation applied to detecting change in peripheral nerve in periods of some milliseconds (213) do not yet appear to have been applied to the central

nervous system, but a method permitting study during periods of a second or so have been described (74, 77, 147).

### *Analytical Notes*

Fixing and extracting central nervous tissues for analysis have employed many of the commonly used reagents. Trichloroacetic acid has been used extensively to obtain 'acid-soluble phosphates' (76, 112, 138, 194). Analysis for these compounds from cerebral tissues meets special problems which require careful consideration (76, 194). Trichloroacetic acid has been employed in preparation for nucleic acid analyses (116, 196). 'Phosphoprotein' from cerebral tissues also requires special care in interpretation of analytical values (48, 76, 196).

Perchloric acid has been employed to yield acid-soluble phosphates and has the virtue of yielding a clear solution from which the excess perchlorate can be largely removed as the potassium salt at 0°C; this is important in subsequent assays using enzymic methods (100) or ion exchange (186). As a protein precipitant and agent for extracting nucleotides, perchloric acid has the advantage over trichloroacetic acid of not absorbing light at wavelengths about 260 mμ, although when hot it may extract other substances which absorb strongly at about 275 mμ (116).

Tungstic acid (20 mmole) is an effective extractant of cerebral tissues for chloride analysis (208) as is sulphosalicylic acid for glutathione. Hot ethanolic potassium hydroxide, as commonly used in determining glycogen in other tissues, yields from cerebral tissues a glycogen precipitate contaminated with carbohydrate-containing lipids which may be removed by washing with chloroform-methanol (91, 109).

## NORMAL METABOLIC CHARACTERISTICS

### *Water and Electrolytes*

When cerebral slices are cut and incubated aerobically in salines, there is an increase in weight of up to 50 per cent of that of the original slice within 1 hr. (40, 162, 177, 191). Although this increase has been ascribed variously to an increase in intracellular water (4) and in extracellular water (191), it has recently been shown (108, 162) that the fluid entering the tissues is not water alone but a solution approximately isotonic with the medium. The problem has been reinvestigated by Pappius & Elliott (162) using thiocyanate, sucrose and inulin to determine the volume of the extracellular space. These agents are assumed not to enter the cells and consequently the amount taken up from solution by a slice under differing conditions affords a measure of the extracellular volume. It was found that aerobic swelling in a glucose bicarbonate medium was due to an increase in the extracellular space, the 'nonthiocyanate nonsucrose' space remaining reasonably constant. The inulin space was much less than the thiocyanate space (41). The suggestion that this is owing to the inulin molecule being too large to enter the whole of the extracellular space is difficult to reconcile with the finding of Stern and co-workers (191) that glutamo-aspartic transaminase, an enzyme of molecular weight 60,000, can readily diffuse out of tissue slices. It was concluded (162, 163) that swelling involves an uptake of fluid which need not be continuous with the medium.

Suppression of swelling by including high concentrations of sucrose or of polyvinylpyrollidone in the medium reduces the intracellular space but not the extracellular space. Swelling increases if slices are incubated anaerobically (162, 191), the increase being intracellular, suggesting that energy is essential for the maintenance of the size of the intracellular space.

Studies of the distribution of salts, such as potassium salts, between the fluid and the tissue slice show a similar dependence upon energy-yielding processes and other factors. Thus under anaerobic conditions or immediately after cutting and placing in saline, cerebral slices lose from 50 to 70 per cent of their total potassium (162, 204). Under aerobic conditions, the addition of glucose to the medium assists the reaccumulation of some of the lost potassium. Under anaerobic conditions glucose alone cannot support such a recovery and glycolysis must be stimulated by the addition of pyruvate to promote even a small recovery of lost potassium (163).

The greatest reaccumulation of potassium occurred if glutamate, but not glutamine, was added to the medium containing glucose (204). Glutamate alone was not more effective than glucose alone. Of all other amino acids tested only aspartic acid could replace glutamate presumably because of its conversion to glutamic acid in the tissue slice. The role of glutamate is not clear. Since an equivalence exists between the amounts of glutamate and potassium accumulated by the slice, it is possible that the γ-carboxyl group is essential to potassium transport. Glutamate causes swelling owing to an increase in the intracellular space (163) and it has been calcu-

lated that if the potassium in the slice is all in the intracellular space, then, under such conditions, uptake of potassium does not involve an increase in intracellular potassium concentration.

Although glutamate increases the level of potassium in the slices, Korey (96) found that it did not promote an increased rate of exchange of radioactive potassium between cat cerebral slices and the surrounding medium. Under conditions where potassium accumulation is optimal, this exchange involves some 3.5 to 4 per cent of the total tissue potassium per min. (104). It has generally been assumed in such calculations that all the potassium of cerebral slices is readily exchangeable, but some contrary evidence exists. Thus it has been calculated (89) from the data of Krebs *et al.* (104) that in adult cerebral tissue a proportion of the total potassium has a low rate of turnover as compared with the remainder. Such slowly exchangeable potassium may be bound to phospholipids (50) for this fraction is absent in the infant unmyelinated rat brain (89). It has also been shown (193) that part of the potassium of homogenates of cerebral tissues does not pass through an ultrafilter whereas the cerebral sodium salts are readily filtered.

*Carbohydrate*

Carbohydrate metabolism is of outstanding importance to the central nervous system. For this reason it has been frequently and adequately reviewed, and the function of the present section is solely to quote such accounts. Individual enzyme processes of glycolytic and oxidative sequences, studied specifically in central nervous system preparations, have been detailed from the point of view of their quantitative requirements for substrates and cofactors and, especially, rates of reaction (136, 171). Respiration and glycolysis as organized sequences have been described (43, 88, 136, 224), including methods of study, normal values in many mammalian species, substrates, aerobic and anaerobic processes. Factors conditioning the balance between aerobic and anaerobic processes have been appraised quantitatively (136). The variation in level of carbohydrate metabolism with change in functional activity has been quantitatively expressed and mechanisms of the adjustment appraised (136). The development of processes of carbohydrate metabolism in the growing nervous system has been reviewed (136, 215) both with respect to individual enzyme reactions, and also to the over-all processes in cell-containing tissues. Many apposite comparisons have been made between the carbohydrate metabolism of the brain *in vivo* and *in vitro* (43, 80, 136).

*Amino Acids and Proteins*

Although cerebral tissues *in vivo* are well known to contain almost all the known amino acids in a freely extractable form (220) or combined as protein (16, 170), with the exception of glutamic acid and compounds related metabolically little is known of cerebral amino acid metabolism *in vitro* and still less of protein metabolism. Slices of rat or guinea-pig cerebral tissue in a phosphate or bicarbonate saline were unable to oxidize any of 13 naturally occurring amino acids other than L (+) glutamate (101, 102, 216) when these were added singly to the tissue preparation. With human cerebral tissue and amino acid mixtures, the situation appears to be more complex. Thus a mixture of amino acids containing glutamate failed to maintain the respiration of cerebral cortical slices over a period of 3 hr., although glutamate at a level identical with that in the mixture prevented such a decrease (45). The initial oxygen uptake with the amino acid mixture was similar to that obtained with pyruvate as the substrate. It was suggested that either the oxidation of glutamate in a mixture is modified by the presence of other amino acids or is not solely responsible for the oxygen uptake of slices respiring in such a mixture.

Failure to metabolize certain amino acids may be partly due to permeability barriers, for rat cerebral tissue homogenates oxidatively decarboxylate or deaminate L-valine (51), DL-alanine (55), DL-phenylalanine, L-tryptophane, D-histidine, L-arginine and L-lysine (37). Metabolism ceased when the atmosphere of oxygen was replaced by nitrogen. The carbon of glycine is metabolized by at least two routes. Thus the carboxyl carbon was metabolized largely via decarboxylation while the methyl carbon was incorporated largely into the residue remaining after extraction of lipids and compounds soluble in trichloroacetic acid. This residue was considered to be protein (111) but would also contain nucleic acids, nucleoprotein and probably proteolipid. The decarboxylase system was associated with particulate material and was not operative in acetone powders. This is in contrast to the alanine decarboxylase system which was equally active in both homogenates and acetone powders (56).

It is probable that *in vitro* at least, a major source of the carbon in certain of the free cerebral amino acids derives from glucose. With rat cerebral cortex slices

metabolism of uniformly labelled $C^{14}$ glucose gave rise to labeled glutamic and aspartic acids within 2 to 4 min. of incubation, followed by incorporation into γ-aminobutyric acid (14). After incubation for 1 hr. in a phosphate buffered medium, 9 per cent of the glucosed metabolized was present as glutamic acid, 3 per cent as γ-aminobutyric acid and 2.4 per cent as aspartic acid. The remainder was accounted for as lactic acid and carbon dioxide. No other labeled amino acids except a trace of alanine were detected. Formation of these amino acids may be the starting point for the synthesis of other amino acids and possibly proteins of the central nervous system. Thus *in vitro* experiments with minced brain from 1-day-old mice showed that in 24 hr. the carbon of uniformly labeled $C^{14}$-glucose was distributed in all the amino acids of cerebral proteins with the exception of proline and threonine. On the basis of previous work (169) the authors considered that such labeling could not be due to incorporation of radioactive carbon dioxide produced during the experiment, but the evidence provided in support of this view is not wholly convincing.

GLUTAMIC ACID. Since the role and importance of glutamic acid in the metabolism of the central nervous system has been the subject of several recent reviews (136, 209, 210, 214, 219, 220), comment here will be restricted to major points and to recent developments.

Glutamic acid together with its amide glutamine constitute up to 80 per cent of the free α-amino nitrogen of cerebral tissues. Slices of cerebral cortex in a phosphate or bicarbonate buffered saline were able to maintain a concentration gradient of glutamic acid provided glucose was present in the saline as an energy-yielding substrate (191). Other substrates such as fructose, lactate or pyruvate also assisted accumulation but were not as effective as glucose. Glutamate alone could not maintain the tissue concentration of glutamic acid; neither could anaerobic glycolysis unless adenosine triphosphate was added to the medium. In slices, homogenates or in particulate preparations, glutamate has been shown to undergo a variety of reactions which include: *a*) conversion to glutamine (44, 101, 102, 113, 191); *b*) decarboxylation to yield γ-aminobutyric acid (172, 209); *c*) oxidative deamination to yield α-oxoglutaric acid and ammonia (30, 34, 216); *d*) transamination principally with oxaloacetic acid (28) but also with other α-keto acids (173); *e*) exchange of the amido group with other amines in the glutamotransferase reaction (105, 181), a process requiring energy in the form of adenosine triphosphate; and *f*) transpeptidation (49, 70) whereby the glutamyl group of glutathione is transferred to other amino acids, thus forming glutamyl peptides. The multiplicity of reactions undergone assigns to glutamic acid a place of importance in the central nervous system, both as a means of controlling the intracellular concentration of ammonia and possibly as a source of amino groups in the synthesis of protein.

Much recent work concerns the production, possible function and fate of γ-aminobutyric acid. In the animal body this amino acid is found in appreciable concentration almost solely in nervous tissue (175) and is formed at a rate, calculated from the data of Roberts & Frankel (174), reaching 30 μmoles per gm wet wt. tissue per hr. under optimal conditions. It has been shown (13, 42) that γ-aminobutyric acid is identical with a factor, extracted from brain, which reversibly blocks stretch receptor neurons of the crayfish. γ-Aminobutyric acid was shown to be synthesized and to exist in brain in a form not available for this reaction (called by Elliott and collaborators an 'occult' form), but is released by boiling in water, by dilute hydrochloric acid or by alkali. It is suggested that γ-aminobutyric acid may be the transmitter substance of inhibitory neurons. Such a role is in keeping with its existence in an 'occult' form and requires also that the acid be metabolized to less active products. In this latter connection the major metabolic route probably is transamination with α-oxoglutarate to form succinic semialdehyde and glutamic acid (15, 173).

AMMONIA FORMATION. As mentioned above one function of the glutamine-glutamic system probably is the removal of excess ammonium ions from the tissue, a fact which raises the problem of the origin of such ammonia. Cerebral slices, when incubated in a phosphate or bicarbonate saline in the absence of substrate, evolve ammonia over a period of several hours (219, 223) without any signs of the production coming to an end. Ammonia formation is inhibited by anaerobic conditions or by inhibitors which affect oxidative phosphorylation or electron transport. Production is inhibited also by glucose.

Attempts to assign such formation to the activity of nucleoside and nucleotide deaminases (92, 152, 222, 223) have shown that this route of formation is unlikely, particularly in view of the relatively small amounts of nucleotides present in the tissue. The other known deamination systems of cerebral tissue, viz. glutaminase, glutamic dehydrogenase and amine

oxidase, were considered on various grounds to be ruled out in the production of ammonia (222). Deamination of amino acids was found not to occur with cerebral suspensions (222). It was suggested that ammonia arises from some reaction linked to proteolysis but as yet no convincing evidence has been produced in support of the view. Several active proteinases and peptidases exist in cerebral tissue (6, 7, 93, 164).

*Phosphates*

Although studied *in vivo* in relation to functional activity since the 1940's, the investigation of phosphate metabolism in cerebral tissue *in vitro* is largely of more recent origin (76, 128). It is convenient here to consider some of the various aspects of metabolism under two headings, in tissue slices and in disintegrated preparations. Phosphate intermediates in relation to carbohydrates will not be considered.

METABOLISM IN TISSUE SLICES. Cerebral tissues have been shown to contain a large number of phosphorus derivatives, some of which can be extracted by reagents such as trichloroacetic acid and include creatine phosphate, adenosine triphosphate and inorganic phosphate as the major constituents. Others insoluble in trichloroacetic acid include all the phospholipids, nucleic acids, phosphoprotein and phosphoinositides. Derivatives of cytidine, uridine and guanosine phosphates have also been isolated and characterized (75, 76, 182, 207).

When freshly cut, cerebral slices contain low levels of creatine and adenylphosphates and a high level of inorganic phosphate; but on incubation in a suitable oxygenated saline containing glucose, levels of creatine phosphate and adenosine triphosphate rise while the level of inorganic phosphate decreases (100, 138). Although under such conditions the levels of 'energy-rich' phosphates do not rise to more than 50 per cent of the levels normally found *in vivo*, the level of creatine phosphate can be increased to 70 per cent of the *in vivo* level in 2 hr. by including creatine in the incubation medium (206). Maintenance of adequate levels of creatine phosphate in the slice is dependent upon a supply of oxygen and glucose (129) or of pyruvate (76), other substrates such as citrate, succinate, fumarate and glutamate failing to support resynthesis. The failure of glutamate, even in the presence of glucose, to maintain the level of creatine phosphate is curious in view of its effect in maintaining the potassium concentration of tissue slices and of its existence free in the tissue *in vivo* at approximately 10 mmole (220). It has been shown that the $\gamma$-phosphorus of adenosine triphosphate is the precursor of the phosphorus of phosphocreatine, the latter having a turnover rate of about 160 to 170 $\mu$mole per gm wet wt. tissue per hr. (76). Attempts to promote the synthesis of phosphopyridine dinucleotide by inclusion of possible precursors in the medium were unsuccessful (65).

Metabolism of other phosphate derivatives such as phospholipids, nucleic acids and phosphoprotein has been shown to be an active process. Thus radioactive phosphate is incorporated into cerebral phospholipids (46, 57, 197) in the presence of oxygen and glucose but not in the absence of glucose or under a nitrogen atmosphere in the presence of glucose.

The *in vitro* phosphate metabolism of nucleic acids and phosphoproteins has been investigated (33, 75, 197). Incorporation of radioactive phosphate into phosphorus considered to arise from phosphoprotein was shown to proceed at a rate greater than incorporation into other groups of acid-insoluble phosphates. Incorporation into nucleic acids was slow and took place almost exclusively into ribose nucleic acid, little or no activity occurring in deoxyribose nucleic acid. It is reported (179) that the inositol phosphorus of the tissue residue after removal of acid-soluble phosphates and phospholipids also exhibits a marked turnover. As with energy-rich phosphates, substrates such as succinate, malate, glutamate and $\alpha$-oxoglutarate failed to support incorporation of radioactive phosphorus into phospholipids, nucleic acids and phosphoprotein of cerebral slices. Pyruvate and lactate supported incorporation to a degree less than glucose. Anerobiosis abolished incorporation of phosphate into any fraction.

METABOLISM IN DISINTEGRATED PREPARATIONS. Disruption of cellular structure permits the intermingling of cellular components and consequently many phosphates essential to metabolism are readily degraded. Thus adenosine triphosphate is rapidly converted to adenylic acid and inorganic phosphate by the combined action of adenosine triphosphatase and myokinase (66, 119, 150, 160). The adenosine triphosphatase system involves at least two enzymes, one activated by magnesium ions and inhibited by calcium ions and the other activated by calcium ions (155). It is not identical with the inorganic pyrophosphatase system of brain (66, 165). Di- and triphosphopyridine nucleotides are degraded by an enzyme specific for the oxidized forms (145), the breakdown being inhibited by nicotinamide (121).

Degradation of creatine phosphate does not occur in dilute homogenates of cerebral tissues by a simple hydrolytic mechanism but requires the addition of adenylic acid or adenosine diphosphate (157, 160). Under these conditions adenosine diphosphate is converted to the triphosphate while creatine phosphate is degraded to creatine.

PHOSPHATE SYNTHESIS AND OXIDATIVE PHOSPHORYLATION. It was early recognized (12) that inorganic phosphate and adenylic acid were essential for the oxidation of pyruvic acid by dialyzed pigeon brain. Further examination by Ochoa revealed that during such oxidation considerable quantities of labile phosphate, presumably adenosine triphosphate, were formed. In the presence of sodium fluoride to inhibit adenosine triphosphatase, some two to three atoms of phosphorus were esterified for each atom of oxygen consumed, yielding P/O ratios of two to three (25, 110, 159).

Since oxidative phosphorylation is a primary step in aerobic cellular metabolism, it is to be expected that factors inhibiting or accelerating it would also affect the metabolism of the integrated tissue. Among such factors are levels of inorganic phosphate and creatine phosphate. Literature relating to the effects of different levels of inorganic phosphate has been summarized elsewhere (76, 128) and parallelism shown to exist between the concentrations of inorganic phosphate inducing marked oxygen uptake in homogenates and those existing in cerebral tissues *in vivo* in different physiological states. Levels of phosphate acceptors such as adenine derivatives, creatine or glucose (12, 64, 159) have similarly been shown to affect the rate of oxygen uptake.

As might be expected by analogy with other tissues, mitochondrial preparations from cerebral tissues carry out oxidative phosphorylation with a number of substrates (1, 22) which include the intermediates of the tricarboxylic acid cycle and glutamic acid. With such substrates the majority of P/O ratios were 2.0 or greater. The phosphorylative activity is more stable at 18° than at 37°C (22), and attempts have been made to find the causes of instability at the higher temperature (24, 59).

### *Lipids*

The state of knowledge of the metabolism of brain lipids *in vitro* up to the autumn of 1951, was covered by an earlier review from this laboratory (185). Later discoveries were described by Rossiter (180), Lynen (120) and Klenk (95). The synthesis of some highly unsaturated fatty acids (196) and the oxidation of carboxyl-labeled octanoate, laurate (8, 61, 84) and palmitate added *in vitro* have by now been demonstrated with some certainty in brain slices and homogenates with the aid of $C^{14}$; the $\beta$-ketoacyl-thiolase, acylcoenzyme A-deacylase and $\beta$-hydroxy-acyl dehydrogenase activities of brain have been detected and measured (95); but the evidence for the oxidation of intrinsic fatty acids by brain slices or homogenates, whether in the form of $C^{14}O_2$ from fatty acids given ante mortem by stomach tube or of a special breakdown product of unsaturated fatty acids cannot be considered quite as significant (29). Work with $C^{14}$ has also shown that added fatty acids are slowly incorporated into the lipids of respiring brain slices and homogenates in the presence of coenzyme A (84). The metabolism of cholesterol in the central nervous system is confined, so far as is still known, to the brains of embryos or young animals during myelination (185), and the metabolism of cerebrosides and gangliosides in the central nervous system remains largely unknown. Strandin (52) is now believed to be a mixture of gangliosides with a small proportion of mucopolysaccharides (178, 201, 202). Unpublished work in these laboratories by Sloane-Stanley has not confirmed an earlier announcement (205) of a 'cerebrosidase' in brain. Nothing appears to be known of the metabolism of sulphatides *in vitro*.

The breakdown and synthesis of phospholipids, or at least the removal and reattachment of their polar groups, have been studied more thoroughly (cf. 5). Perhaps the only enzymic reaction of a brain lipid known to be as rapid as, say, brain respiration (60 $\mu$moles per hr. per gm fresh tissue) is still the hydrolysis of diphosphoinositide into organic phosphate, inositol monophosphate and acid-insoluble residues (184, 186). This reaction has now been shown to occur in at least two independent steps, one of which is activated by calcium and can proceed at a rate of 300 $\mu$moles per hr. per gm fresh tissue or more (176). The synthesis of diphosphoinositide in brain slices and homogenates has also been detected by following the incorporation of $P^{32}$ into the 'inositol diphosphate' isolated by paper chromatography from the products of alkaline hydrolysis of the lipids extracted from the tissues after precipitation with trichloroacetic acid, or from an alkaline or acid hydrolysis of the precipitate (31, 32). The incorporation was shown to need the energy supplied by respiration or glycolysis, and to be very much more rapid

(by a factor of 10 to 100) than the incorporation of $P^{32}$ into the partial hydrolysis products (glyceryl-phosphoryl-choline, -serine and -ethanolamine) of the other phospholipids. There was no change in the absolute quantity of 'inositol diphosphate' obtained under conditions making for wide variations in its specific radioactivity; its synthesis must therefore have been accompanied by an equally rapid breakdown of the intrinsic diphosphoinositide in the tissue. In all these experiments, another phosphate ester, believed to be derived from a phosphatidic acid, became labeled even more rapidly than 'inositol diphosphate'; Witter (225) has pointed out that this may be an occurrence peculiar to work *in vitro*, since this compound has not been found in experiments with intact animals.

It appears that the much slower biosyntheses of the better-known nitrogenous phosphatides (lecithin, phosphatidylethanolamine, phosphatidylserine and sphingomyelin) follow much the same routes as in other tissues; and in slices, lecithin incorporates $P^{32}$ more rapidly than phosphatidylethanolamine or phosphatidylserine, while in homogenates phosphatidylserine is the most active of these three (180). The mechanism of the synthesis of diphosphoinositide is still largely unknown, but it appears that the inositol diphosphate moiety (51) has a much more rapid turnover than the rest of the molecule, since the rate of incorporation of $C^{14}$-labeled glycerol into lecithin and all the kephalins is about the same (82). Autolyzing brain slices have also been found to lose 'kephalin' and 'sphingomyelin,' but not other lipids, at significant rates (85) which confirms the work of Tyrrell (211), Goebel & Seekfort (63) and Sperry (189). It has been shown that the cations associated with diphosphoinositide and other acidic lipids can be readily exchanged for others (53, 188).

## METABOLISM MODIFIED BY APPLIED AGENTS

### *Electrical and Cognate Influences*

Detailed assessments of the effects of applied electrical impulses upon the *in vitro* metabolism of carbohydrates and phosphates together with surveys of the literature have been published (76, 134, 136). Generally, application of alternating electrical potentials to slices or chopped preparations of cerebral tissues which retain cellular structure [but not to other tissues (98)] results in increases of the order of 100 per cent in the oxygen uptake and aerobic lactic acid production. Levels of creatine phosphate fall while those of inorganic phosphate rise. Anaerobic glycolysis is decreased. Examination of the sequence of these reactions has revealed that the most rapid events are the breakdown of creatine phosphate and an increase in the levels of inorganic phosphate. Increase in lactic acid accompanies the change in phosphates but glycogen levels are not affected (147). The changes are rapid and occur within 2 sec. of applying electrical pulses. No response is obtained with homogenates or preparations of cerebral mitochondria. Owing to the nature of the technique used to measure rapid changes in levels of the intermediates, no accurate measurement of the rate of onset of oxygen uptake has been made; but increased uptake probably commences within 20 sec. of switching on the pulses. On switching off, creatine phosphate is rapidly resynthesized at 150 μmoles per gm. wet wt. per hr., and the increased levels of tissue lactic acid return to normal (73, 147). The rates of change of the phosphates and lactic acid are high. Thus creatine phosphate is metabolized at 1200 to 1400 μmoles per gm wet wt. per hr., while inorganic phosphate increases at about 800 μmoles P per gm wet wt. per hr. Lactate is formed at a rate of 420 μmoles per gm per hr. Consideration of these rates in relation to the maximal oxygen uptake of cerebral tissues under the influence of applied pulses (some 100 μmoles $O_2$ per gm wet wt. per hr. for slices of guinea-pig cerebral tissue) shows that the rate of breakdown of creatine phosphate cannot be accounted for on the assumption (3) that the decrease is solely due to inhibition of oxidative phosphorylation by the pulses. Examination of the pathway of creatine phosphate breakdown by radioactive tracer techniques (74, 75) has shown that other cerebral constituents, including adenosine triphosphate, guanosine triphosphate and 'phosphoprotein,' are involved in an exchange reaction which is likely to proceed at the rate of creatine phosphate breakdown.

In view of the influence of inorganic phosphate and of phosphate acceptors, such as creatine, upon oxygen uptake in tissue preparations described above, it is understandable that increase in their levels should lead to increased oxygen uptake of intact cerebral slices. In this respect the effect of electrical pulses may be regarded as removing a constraint imposed upon metabolism by the lowered levels of inorganic phosphate and acceptors which normally exist within the slice, permitting the tissue to exhibit its maximal metabolic potential.

*Potassium and Other Ions*

Increasing the concentration of potassium salts in normal salines to 0.1 M causes respiration and aerobic glycolysis to increase by about 100 per cent (9). Substrates which support increased oxygen uptake include glucose, fructose, lactate and pyruvate, but not members of the tricarboxylic acid cycle (35, 115). As with electrical pulses anaerobic glycolysis is decreased (35). The effect is not specific to the potassium ion and is given, although to a markedly lesser degree, by lithium, rubidium and caesium ions (35). Sodium salts are ineffective (35, 36, 141). Although the effect is most marked at a concentration of 0.1 M, it is readily detectable at 0.02 M (9, 141). In addition to increasing oxygen uptake and aerobic glycolysis, potassium salts at 0.03 M increase free acetylcholine production in cerebral slices (122). In higher concentrations, levels of creatine phosphate are decreased (73, 141).

The mechanism of the effect is not clear. Potassium ions are known to increase the rate of conversion of phosphoenolpyruvate to pyruvate by accelerating the phosphorylation of adenylic acid to adenosine triphosphate (153). It has been suggested that in their presence an increased quantity of pyruvate is thus made available for oxidation (115) and an increased formation of adenosine triphosphate ensues (62). These proposals are unlikely since pyruvate itself does not yield maximal rates of oxygen uptake when used as sole substrate, and levels of creatine phosphate, linked with those of adenosine triphosphate, are decreased by 0.1 M potassium salts. It seems more reasonable to suppose that increased potassium salts act by depolarization of the neuronal membrane (129) in a manner analogous to that suggested for electrical pulses. The increased metabolism is thus a reflection of the increased energy expenditure involved in restoration of the more normal state. Effects of potassium, and other ions considered here, upon individual enzyme systems or on metabolism of particulate preparations are outside the scope of this article, but it is of interest to note in passing that oxygen uptake of cerebral mitochondria is not affected by concentrations of potassium chloride ranging from 0.02 MM to 50.0 MM (158).

Changes of metabolism of tissue slices with other ions have been noted. Thus decreasing the levels of calcium salts in the medium, increases the oxygen uptake (103) but decreases anaerobic glycolysis (167). On the other hand increasing the calcium level to 0.082 M had no effect upon respiration, aerobic glycolysis or levels of creatine phosphate (141). In the absence of sodium ions oxygen uptake and aerobic glycolysis are decreased, together with levels of creatine phosphate (141). In such media slices show no response to electrical pulses. Ammonium salts at 0.03 M increase oxygen uptake and aerobic glycolysis, and decrease levels of creatine phosphate (141, 218) and rates of phospholipid metabolism (180), analogous to the effect of potassium. However, the ammonium effect is detectable at 0.3 MM, some hundred times lower than that of potassium required for the same effects. At levels of 0.05 M ammonium salts, acetylcholine production is inhibited (122). Little effect was detected at lower levels.

*Metabolic Inhibitors*

Elucidation of metabolic pathways or the mechanisms involved in a given reaction has been greatly assisted in disintegrated preparations by the use of agents inhibiting one, or at the most two, particular enzyme systems to a marked degree while having little effect upon others. As a result, study of the effects upon cerebral metabolism of inhibitors with a known point of action has been carried out by many workers in attempts to correlate such effects with those of known therapeutic agents. Of the inhibitors used to demonstrate the participation of energy-yielding processes in metabolism of the central nervous system, probably the best known are fluoride, iodoacetic acid, malonic acid, cyanide, azide and 2,4-dinitrophenol.

With cerebral tissue slices in the presence of increasing concentrations of inhibitors such as fluoride and iodoacetate, which primarily block the conversion of glucose to pyruvate, both respiration and glycolysis decrease. Inhibitors, such as malonate or cyanide which act at points in the conversion of pyruvate to carbon dioxide and water, decrease oxygen uptake and increase glycolysis (72, 192). Dinitrophenol, which prevents the permanent esterification of adenyl derivatives to adenosine triphosphate and in consequence maintains high concentrations of inorganic phosphate and phosphate acceptors within the tissue, increases both oxygen uptake and glycolysis (141). Azide, which has a similar effect upon oxidative phosphorylation in liver preparations (117), also inhibits the cytochrome system (90) and decreases levels of energy-rich phosphate, aerobic glycolysis and oxygen uptake (99).

Systems sensitive to agents such as the above might be expected to be most easily detectable under con-

ditions in which they operate at their maximum rate. Situations giving rise to this are those brought about by electrical pulses and increased potassium salts. With cerebral tissues stimulated by electrical pulses, iodoacetic acid at $10^{-5}$ M inhibited aerobic glycolysis at concentrations which had little effect upon the increased oxygen uptake (72). Increasing concentrations of the inhibitor to $5 \times 10^{-5}$ M reduced the stimulated oxygen uptake to levels found in unstimulated tissue but did not further reduce lactic production. At this concentration no effect was observed upon the stimulated oxygen uptake with lactate as substrate. Malonate at $10^{-3}$ M increased stimulated lactic acid production markedly while affecting oxygen uptake only slightly. Azide was found to depress stimulated oxygen uptake and to increase lactic production (99). Here also, as with the other inhibitors used, the effects noted with stimulated metabolism were obtained with concentrations of inhibitors which were without effect upon the metabolism of unstimulated tissues. Iodoacetic acid at its lowest concentration was an exception to this. Similar results have been obtained with 0.1 M KCl as the stimulating agent and fluoride or malonate (94) as inhibitor. A curious feature of the action of malonate is its inability to inhibit the oxygen uptake of slices in the presence of lactate as substrate at concentrations which are effective when glucose is the substrate (69, 72, 217).

Results such as the above fit well into the integrated metabolic patterns existing in intact cerebral slices. Thus the effects of iodoacetate are in harmony with a partial metabolic block of 3-phosphoglyceraldehyde dehydrogenase, the limited quantity of pyruvate formed being oxidized preferentially rather than being reduced to lactate. The effect of azide can be interpreted as the result of a balance between inhibition of oxygen uptake and increased levels of phosphate acceptors and inorganic phosphate. A discussion of changes resulting from inhibition of a single enzymic step in cerebral metabolism has been given by Racker & Krimsky (168).

### *Therapeutic and Toxic Agents*

Commencing with toxic agents having better understood effects, cyanide *in vivo* produces metabolic effects analogous to those of anoxia, namely decreased oxygen uptake, decreased creatine phosphate, and increased levels of lactic acid and inorganic phosphate. Concentrations bringing about these changes were estimated to be $10^{-5}$ M. *In vitro* such concentrations were without effect upon the respiration glycolysis of minced brain tissue. Higher concentrations of $10^{-4}$ M markedly reduced oxygen uptake and increased lactic acid production of cerebral tissue slices.

Anticholinesterases have attracted much work (215). Of them, diisopropyl fluorophosphonate (DFP) is probably outstanding in forming a difficultly reversible combination with acetylcholine esterase. In cerebral tissue from rabbits succumbing to a lethal dose, the cholinesterase activity was completely inhibited. In hens paralysis accompanied by demyelination of the spinal cord and peripheral nerve has been found following moderate doses. The excitatory effects in man and other animals may be due to the higher concentrations of cerebral acetylcholine existing in the presence of the inhibitor. DFP and other anticholinesterases including physostigmine have been used to study a possible relationship between cholinesterase activity and potassium transport in cerebral slices (198, 199). It was found that concentrations which completely inhibited cholinesterase activity in chicken cerebral tissue slices were without effect upon potassium loss from the slices. Concentrations inducing potassium loss also inhibited oxygen uptake in slices and oxidative phosphorylation in homogenates, suggesting that potassium loss was due to impairment of energy-producing mechanisms. Among other anticholinesterases physostigmine has been widely used to study the acetylcholine metabolism of nervous tissue. At $10^{-4}$ M no major effect was detected upon the electrically stimulated metabolism of cerebral slices (127). Such effects are unlikely since phenomena associated with transmission of impulses are not likely to be apparent in an experimental arrangement where pulses are applied directly to the greater part of the tissue. Prolonged electrical stimulation of cerebral slices in the presence of physostigmine leads to accumulation of acetylcholine in the medium. The differential effect of DFP and other anticholinesterases upon the esterases of cerebral tissue has been used to distinguish between the various types present in rat brain homogenate (154).

It is now well established that the toxic properties of fluoroacetate *in vivo* are due to conversion to fluorocitrate followed by an action of fluorocitrate in blocking cerebral aconitase. In pigeon brain particulate preparations, fluorocitrate blocks the oxidation of pyruvate with accumulation of citrate (58). Elucidation of this mechanism has not yet led to a full understanding of the toxic action of fluorocitrate.

Of other agents, atropine at $8 \times 10^{-4}$ M depressed

response in oxygen uptake and lactic acid production of electrically excited cerebral tissue slices but had no effect upon unstimulated tissue nor on tissue treated with potassium salts or 2,4-dinitrophenol (127). Lysergic acid diethylamide, mescaline and ergotoxin similarly affected stimulated metabolism at concentrations ineffective upon unstimulated respiration (114). Other agents affecting cerebral metabolism *in vitro* include snake venoms, the neurochemical effects of which have been discussed by Braganca (18).

The very considerable literature concerning therapeutic agents and cerebral metabolism has been discussed elsewhere (81, 83, 136). Brief comment here is confined to a few depressants and anticonvulsants as examples of the biochemical problems encountered in investigating centrally acting drugs. *In vitro* studies have been carried out largely in systems with intact cells and only a few in systems in which the cells have been broken down.

Recent work with electrically stimulated nervous tissue has indicated ways in which depressants *in vivo* decreased respiration and lactic acid production, and increased levels of creatine phosphate. With cerebral tissue slices, in which the metabolism was increased by electrical pulses, potassium salts and 2,4-dinitrophenol, it was shown (131) that depressants such as phenobarbital, butabarbital and chloral at $10^{-4}$ M decreased the stimulated respiration markedly and the stimulated lactic-acid production slightly, while having no effect upon unstimulated metabolism. Anticonvulsants have similarly been examined (54, 67), and interesting differences noted between them and depressants. Thus trimethadione at $10^{-2}$ M had no effect upon respiration stimulated by low-frequency condenser pulses, but at $10^{-3}$ M suppressed respiration stimulated by high frequency sine-wave pulses. A general depressant such as butabarbital depressed the respiration stimulated by both types of pulses. The increased lactate formation was generally less susceptible to the action of these agents than was oxygen uptake. Bromide, the *in vivo* effects of which are related to chloride concentration, has been examined *in vitro* in a chloride-free medium (208). Concentrations up to 50 mM did not effect cerebral tissues as regards response to condenser pulses or to stimulation with potassium nitrate. However, like trimethadione, bromide at $2 \times 10^{-2}$ M inhibited respiration increased by high frequency pulses (54). In the superior cervical ganglion of the rabbit it has been established that clinically effective concentrations of depressants block synaptic transmission and also diminish the increased oxygen uptake resulting from applied electrical pulses, although having no effect upon the resting oxygen uptake (107). These findings, together with those described above for cerebral tissue slices, make it probable that depressants and anticonvulsants primarily inhibit energy-consuming processes and that the metabolic changes found *in vivo* are in consequence of such inhibition.

Concentrations of general depressants higher than those effective clinically (123) depress the unstimulated oxygen uptake and the levels of creatine phosphate of cerebral slices (24, 33, 128, 136, 151, 203), and numerous studies have sought to establish their action in terms of inhibition of metabolic processes. Concentrations of $10^{-3}$–$10^{-2}$ M decrease both oxygen uptake and lactic acid production in homogenates (68, 166, 203), and also the rate of formation of adenosine triphosphate (25, 39, 86, 87). Similarly concentrations of from 4 to 30 times those effective *in vivo* have been described as 'uncoupling' oxidative phosphorylation in cerebral mitochondrial preparations (11, 20–23). Interference with enzymes directly involved in creatine phosphate and adenosine triphosphate metabolism has not been observed (66, 157).

## REFERENCES


1. Abood, L. G. and R. W. Gerard. *Am. J. Physiol.* 168: 739, 1952.
2. Abood, L. G., R. W. Gerard, J. Banks and R. D. Tschirgi. *Am. J. Physiol.* 168: 728, 1952.
3. Abood, L. G., R. W. Gerard and R. D. Tschirgi. In: *Phosphorus Metabolism*, edited by W. D. McElroy and B. Glass. Baltimore: Johns Hopkins Press, 1952, p. 98.
4. Allen, A. J. *A.M.A. Arch. Neurol. & Psychiat.* 23: 241, 1955.
5. Ansell, G. B. and R. M. C. Dawson. *Biochem. J.* 50: 241, 1951.
6. Ansell, G. B. and D. Richter. *Biochim. et biophys. acta* 13: 87, 1954.
7. Ansell, G. B. and D. Richter. *Biochim. et biophys. acta* 13: 92, 1954.
8. Artom, C. *J. Biol. Chem.* 213: 681, 1955.
9. Ashford, C. A. and K. C. Dixon. *Biochem. J.* 29: 159, 1935.
10. Ayres, P. J. W. and H. McIlwain. *Biochem. J.* 55: 607, 1953.
11. Bain, J. A. *Fed. Proc.* 11: 653, 1952.
12. Banga, I., S. Ochoa and R. A. Peters. *Biochem. J.* 33: 1980, 1939.
13. Bazemore, A., K. A. C. Elliott and E. Florey. *Nature, London* 178: 1052, 1956.
14. Beloff-Chain, A., R. Catanzaro, E. B. Chain, I.

MASI AND F. POCCHIORI. *Proc. Roy. Soc., London. ser. B* 144: 22, 1955.
15. BESSMAN, S. P., J. ROSSEN AND E. C. LAYNE. *J. Biol. Chem.* 201: 385, 1953.
16. BLOCK, R. J. AND D. BOLLING. *The Amino Acid Composition of Proteins and Foods.* Springfield: Thomas, 1945.
17. BOLLARD, B. M. AND H. MCILWAIN. *Biochem. J.* 66: 651, 1957.
18. BRAGANCA, B. M. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield; Thomas, 1955.
19. BRIERLEY, J. B. AND H. MCILWAIN. *J. Neurochem.* 1: 109, 1956.
20. BRODY, T. M. *Pharmacol. Rev.* 7: 335, 1955.
21. BRODY, T. M. AND J. A. BAIN. *Proc. Soc. Exper. Biol. & Med.* 77: 50, 1951.
22. BRODY, T. M. AND J. A. BAIN. *J. Biol. Chem.* 195: 685, 1952.
23. BRODY, T. M. AND J. A. BAIN. *J. Pharmacol.* 110: 148, 1954.
24. BUCHEL, L. AND H. MCILWAIN. *Brit. J. Pharmacol.* 5: 465, 1951.
25. CASE, E. M. AND H. MCILWAIN. *Biochem. J.* 48: 1, 1951.
26. CHAPPELL, J. B. AND G. D. GREVILLE. *Nature, London* 174: 930, 1954.
27. CHRISTIE, G. S., J. D. JUDAH AND K. R. REES. *Proc. Roy. Soc., London. ser. B* 141: 523, 1953.
28. COHEN, P. P. AND G. Z. HEKHUIS. *J. Biol. Chem.* 140: 711, 1941.
29. COLE, B. T. *Proc. Soc. Exper. Biol. & Med.* 93: 290, 1956.
30. COPENHAVER, J. H., W. H. MCSHAN AND R. K. MEYER. *J. Biol. Chem.* 183: 73, 1950.
31. DAWSON, R. M. C. *Biochem. J.* 57: 237, 1954.
32. DAWSON, R. M. C. *Biochim. et biophys. acta* 14: 374, 1954.
33. DELUCA, H. A., R. J. ROSSITER AND K. P. STRICKLAND. *Biochem. J.* 47: 139, 1953.
34. DEWAN, J. G. *Biochem. J.* 32: 1378, 1938.
35. DICKENS, F. AND G. D. GREVILLE. *Biochem. J.* 29: 1468, 1935.
36. DIXON, K. C. *J. Physiol.* 110: 87, 1949.
37. EDELBACHER, S. AND W. O. WISS. *Helvet. chim. acta* 27: 1060, 1944.
38. EDSTRÖM, J. E. *Biochim. et biophys. acta* 12: 361, 1953.
39. EILER, J. J. AND W. K. MCEWEN. *Arch. Biochem. & Biophys.* 20: 163, 1949.
40. ELLIOTT, K. A. C. *Proc. Soc. Exper. Biol. & Med.* 63: 234, 1947.
41. ELLIOTT, K. A. C. *Canad. J. Biochem. & Physiol.* 33: 466, 1955.
42. ELLIOTT, K. A. C. AND E. FLOREY. *XX Internat. Physiol. Congr., Proc.* 268, 1956.
43. ELLIOTT, K. A. C., I. H. PAGE AND J. H. QUASTEL (editors). *Neurochemistry.* Springfield: Thomas, 1955.
44. ELLIOTT, W. H. *Biochem. J.* 49: 106, 1951.
45. ELLIOTT, W. H. AND V. C. SUTHERLAND. *J. Cell. & Comp. Physiol.* 40: 221, 1952.
46. FINDLAY, M., W. L. MAGEE AND R. J. ROSSITER. *Biochem. J.* 58: 236, 1954.
47. FINDLAY, M., R. J. ROSSITER AND K. P. STRICKLAND. *Biochem. J.* 55: 200, 1953.
48. FINDLAY, M., K. P. STRICKLAND AND R. J. ROSSITER. *Canad. J. Biochem. & Physiol.* 32: 504, 1954.
49. FODOR, P. J., A. MEHLER AND H. WAELSCH. *J. Biol. Chem.* 202: 551, 1953.
50. FOLCH, J. *J. Biol. Chem.* 174: 439, 1948.
51. FOLCH, J. *J. Biol. Chem.* 177: 497, 505, 1949.
52. FOLCH, J., S. ARSOVE AND J. A. MEATH. *J. Biol. Chem.* 191: 819, 1951.
53. FOLCH, J. AND G. H. SLOANE-STANLEY. In: *Metabolism of the Nervous System*, edited by D. Richter. New York: Pergamon Press, 1957.
54. FORDA, O. AND H. MCILWAIN. *Brit. J. Pharmacol.* 8: 225, 1953.
55. FRIEDBERG, F. *Biochim. et biophys. acta* 11: 308, 1954.
56. FRIEDBERG, F. AND L. M. MARSHALL. *Biochem. et biophys. acta* 10: 624, 1953.
57. FRIES, B. A., H. SCHACHNER AND I. L. CHAIKOFF. *J. Biol. Chem.* 144: 59, 1942.
58. GAL, E. M., R. A. PETERS AND R. W. WAKELIN. *Biochem. J.* 64: 161, 1956.
59. GALLAGHER, G. H., J. D. JUDAH AND K. R. REES. *Biochem. J.* 62: 436, 1956.
60. GEIGER, A., J. MAGNES, R. M. TAYLOR AND M. VERALLI. *Am. J. Physiol.* 177: 138, 1954.
61. GEYER, R. P., L. W. MATTHEWS AND F. J. STARE. *J. Biol. Chem.* 180: 1037, 1949.
62. GHOSH, J. J. AND J. H. QUASTEL. *Nature, London* 174: 28, 1954.
63. GOEBEL, A. AND H. SECKFORT. *Biochem. Ztschr.* 319: 203, 1948.
64. GORANSON, E. S. AND S. D. ERULKAR. *Arch. Biochem. & Biophys.* 24: 40, 1949.
65. GORE, M. B. R., F. IBBOTT AND H. MCILWAIN. *Biochem. J.* 47: 121, 1950.
66. GORE, M. B. R. *Biochem. J.* 50: 18, 1951.
67. GREENGARD, O. AND H. MCILWAIN. *Biochem. J.* 61: 61, 1955.
68. GREIG, M. E. *J. Pharmacol.* 91: 317, 1947.
69. GREVILLE, G. D. *Biochem. J.* 30: 837, 1936.
70. HANES, C. S., F. J. R. HIRD AND F. A. ISHERWOOD. *Biochem. J.* 51: 25, 1952.
71. HARPUR, R. P. AND J. H. QUASTEL. *Nature, London* 164: 693, 779, 1949.
72. HEALD, P. J. *Biochem. J.* 55: 127, 1953.
73. HEALD, P. J. *Biochem. J.* 57: 673, 1954.
74. HEALD, P. J. *Biochem. J.* 63: 242, 1956.
75. HEALD, P. J. *Biochem. J.* 65: 3P, 1957.
76. HEALD, P. J. *Phosphorous Metabolism of Brain.* London: Pergamon Press, 1960.
77. HEALD, P. J. AND H. MCILWAIN. *Biochem. J.* 63: 231, 1956.
78. HEBB, C. O. AND G. M. H. WAITES. *J. Physiol.* 132: 667, 1956.
79. HESSELBACH, M. L. AND H. G. DUBUY. *Proc. Soc. Exper. Biol. & Med.* 83: 62, 1953.
80. HIMWICH, H. E. *Brain Metabolism and Cerebral Disorders.* Baltimore: Williams & Wilkins, 1951.
81. HOAGLAND, H. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955.
82. HOKIN, L. E. AND M. R. HOKIN. *Biochim. et biophys. acta* 18: 102, 1955.
83. HUNTER, F. E. AND O. H. LOWRY. *Pharmacol. Rev.* 8: 82, 1956.

84. Jedeikin, L. A. and S. Weinhouse. *Arch. Biochem. & Biophys.* 50: 134, 1954.
85. Johnson, A. C., A. R. McNabb and R. J. Rossiter. *Canad. J. Res.* 27: 63, 1949.
86. Johnson, J. H. and J. H. Quastel. *Nature, London* 171: 603, 1953.
87. Johnson, J. H. and J. H. Quastel. *J. Biol. Chem.* 205: 163, 1953.
88. Joseph, J. and others. *Guy's Hospital Rep.* 105: No. 1, 1956.
89. Katzman, R. and P. H. Leiderman. *Am. J. Physiol.* 175: 263, 1953.
90. Keilin, D. *Proc. Roy. Soc., London. ser. B* 121: 165, 1936.
91. Kerr, S. E. *J. Biol. Chem.* 116: 1, 1936.
92. Kerr, S. E. *J. Biol. Chem.* 145: 647, 1942.
93. Kies, M. W. and S. Schwimmer. *J. Biol. Chem.* 145: 685, 1942.
94. Kimura, Y. *Sci. Papers Inst. Phys. Chem. Research (Tokyo)* 32: 488, 1940.
95. Klenk, E. In: *Metabolism of the Nervous Systems*, edited by D. Richter. New York: Pergamon Press, 1957.
96. Korey, S. *Biochim. et biophys. acta* 9: 633, 1952.
97. Korey, S. R. and J. D. Nurnberger. *Neurochemistry.* New York: Hoeber, 1956.
98. Kratzing, C. C. *Biochem. J.* 54: 312, 1953.
99. Kratzing, C. C. *Biochem. J.* 62: 127, 1956.
100. Kratzing, C. C. and A. Narayamaswami. *Biochem. J.* 54: 317, 1953.
101. Krebs, H. A. *Biochem. J.* 29: 1620, 1935.
102. Krebs, H. A. *Biochem. J.* 29: 1956, 1935.
103. Krebs, H. A. *Biochim. et biophys. acta* 4: 249, 1950.
104. Krebs, H. A., L. V. Eggleston and C. Terner. *Biochem. J.* 48: 530, 1951.
105. Lajtha, A., P. Mela and H. Waelsch. *J. Biol. Chem.* 205: 533, 1953.
106. Larrabee, M. G. and D. W. Bronk. *Cold Spring Harbor Symp. Quant. Biol.* 17: 245, 1952.
107. Larrabee, M. G., J. G. Ramos and E. Bülbring. *J. Cell. & Comp. Physiol.* 40: 461, 1952.
108. Leaf, A. *Biochem. J.* 62: 241, 1956.
109. Le Baron, F. N. *Biochem. J.* 61: 80, 1955.
110. Lee, K. H. and J. J. Eiler. *J. Biol. Chem.* 203: 705, 1949.
111. Leeper, L. C., V. J. Tulane and F. Friedeborg. *J. Biol. Chem.* 203: 513, 1953.
112. Le Page, G. A. *Meth. med. Res.* 1: 337, 1948.
113. Levitinow, L. and A. Meister. *J. Am. Chem. Soc.* 75: 3039, 1953.
114. Lewis, J. L. and H. McIlwain. *Biochem. J.* 57: 680, 1954.
115. Lipsett, N. M. and F. Crescitelli. *Arch. Biochem.* 25: 329, 1950.
116. Logan, J. E., W. A. Mannell and R. J. Rossiter. *Biochem. J.* 51: 470, 1952.
117. Loomis, W. F. and F. Lipmann. *J. Biol. Chem.* 179: 503, 1949.
118. Lowry, O. H. *J. Histochem.* 1: 420, 1953.
119. Lowry, O. H., N. R. Roberts, K. Y. Leiner, M. L. Wu and A. L. Farr. *J. Biol. Chem.* 207: 1, 1954.
120. Lynen, F. In: *Metabolism of the Nervous System*, edited by D. Richter. New York: Pergamon Press, 1957.
121. Mann, P. J. G. and J. H. Quastel. *Biochem. J.* 35: 509, 1941.
122. Mann, P. J. G., M. Tennenbaum and J. H. Quastel. *Biochem. J.* 33: 1056, 1939.
123. McClennon, H. and K. A. C. Elliott. *J. Pharmacol.* 103: 24, 1951.
124. McIlwain, H. *Biochem. J.* 46: 612, 1950.
125. McIlwain, H. *Biochem. J.* 49: 382, 1951.
126. McIlwain, H. *Biochem. J.* 50: 132, 1951.
127. McIlwain, H. *Brit. J. Pharmacol.* 6: 531, 1951.
128. McIlwain, H. *Biochem. Soc. Sympos.* 8: 27, 1952.
129. McIlwain, H. *Biochem. J.* 52: 289, 1952.
130. McIlwain, H. *J. Neurol. Neurosurg. & Psychiat.* 16: 257, 1953.
131. McIlwain, H. *Biochem. J.* 53: 403, 1953.
132. McIlwain, H. *Proc. Univ. Otago med. Sch.* 32: 17, 1954.
133. McIlwain, H. *J. Physiol.* 124: 117, 1954.
134. McIlwain, H. *Physiol. Rev.* 36: 355, 1956.
135. McIlwain, H. *Biochem. J.* 63: 257, 1956.
136. McIlwain, H. *Biochemistry and the Central Nervous System* (2nd ed.). London: Churchill, 1959.
137. McIlwain, H., G. Anguiano and J. D. Cheshire. *Biochem. J.* 50: 12, 1951.
138. McIlwain, H., L. Buchel and J. D. Cheshire. *Biochem. J.* 48: 12, 1951.
139. McIlwain, H. and H. L. Buddle. *Biochem. J.* 53: 412, 1953.
140. McIlwain, H. and M. B. R. Gore. *Biochem. J.* 50: 24, 1951.
141. McIlwain, H. and M. B. R. Gore. *J. Physiol.* 117: 47, 1952.
142. McIlwain, H. and M. B. R. Gore. *Biochem. J.* 54: 305, 1953.
143. McIlwain, H. and I. Grinyer. *Biochem. J.* 46: 620, 1950.
144. McIlwain, H., H. Martin and M. A. Tresize. *Biochem. J.* 65: 2P, 1957.
145. McIlwain, H. and R. Rodnight. *Biochem. J.* 45: 337, 1949.
146. McIlwain, H., J. Thomas and J. L. Bell. *Biochem. J.* 64: 332, 1956.
147. McIlwain, H. and M. A. Tresize. *Biochem. J.* 63: 250, 1956.
148. McIlwain, H. and M. A. Tresize. *Biochem. J.* 65: 288, 1957.
149. McNabb, A. R. *Canad. J. Med. Sci.* 29: 208, 1951.
150. Meyerhof, O. and N. Geliazkowa. *Arch. Biochem. & Biophys.* 12: 405, 1954.
151. Michaelis, M. and J. H. Quastel. *Biochem. J.* 35: 518, 1941.
152. Muntz, J. A. *J. Biol. Chem.* 201: 221, 1953.
153. Muntz, J. A. and J. Hurwitz. *Arch. Biochem. & Biophys.* 32: 124, 1951.
154. Myers, D. K. *Biochem. J.* 64: 740, 1956.
155. Naidoo, D. and O. E. Pratt. *Biochem. J.* 62: 465, 1956.
156. Naidoo, D. and O. E. Pratt. *Acta histochem. (Jena)* 3: 85, 1956.
157. Narayanaswami, A. *Biochem. J.* 52: 295, 1952.
158. Narayanaswami, A. and H. McIlwain. *Biochem. J.* 57: 663, 1954.
159. Ochoa, S. *J. Biol. Chem.* 138: 735, 1941.
160. Oliver, I. T. *Biochem. J.* 61: 116, 1955.
161. Palladin, A. V., E. Y. Rashba and T. M. Shtutman.

*Ukrain. Biohkim. Zhur.* 23: 265, 1951 (*Chem. Abstr.* 12195, 1954).
162. Pappius, H. and K. A. C. Elliott. *Canad. J. Biochem. & Physiol.* 34: 1007, 1956.
163. Pappius, H. and K. A. C. Elliott. *Canad. J. Biochem. & Physiol.* 34: 1053, 1956.
164. Pope, A. and C. B. Anfinsen. *J. Biol. Chem.* 173: 305, 1948.
165. Pratt, O. E. *Biochem. J.* 55: 140, 1953.
166. Quastel, J. H. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955, p. 648.
167. Quastel, J. H. and A. H. M. Wheatley. *J. Biol. Chem.* 119: 80p, 1937.
168. Racker, E. and I. Krimsky. *J. Biol. Chem.* 173: 519, 1948.
169. Rafelson, M. E., R. J. Winzler and H. E. Pearson. *J. Biol. Chem.* 187: 595, 1949.
170. Rafelson, M. E., R. J. Winzler and H. E. Pearson. *J. Biol. Chem.* 193: 205, 1951.
171. Richter, D. (editor). *Metabolism of the Nervous System.* New York: Pergamon Press, 1957.
172. Roberts, E. In: *Progress in Neurobiology. I. Neurochemistry*, edited by S. R. Korey and J. I. Nurnberger. London: Cassel, 1956, p. 11.
173. Roberts, E. and H. M. Bregoff. *J. Biol. Chem.* 201: 393, 1953.
174. Roberts, E. and S. Frankel. *J. Biol. Chem.* 188: 789, 1951.
175. Roberts, E., S. Frankel and P. J. Harman. *Proc. Soc. Exper. Biol. & Med.* 74: 383, 1950.
176. Rodnight, R. *Biochem. J.* 63: 223, 1956.
177. Rodnight, R. and H. McIlwain. *Biochem. J.* 57: 649, 1954.
178. Rosenberg, A., C. Howe and E. Chargaff. *Nature, London* 177: 234, 1956.
179. Rossiter, R. J. *Canad. J. Biochem. & Physiol.* 33: 475, 1955.
180. Rossiter, R. J. In: *Metabolism of the Nervous System*, edited by D. Richter. New York: Pergamon Press, 1957.
181. Rudnick, D. and H. Waelsch. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 335.
182. Schmitz, H., R. B. Hurlbert and V. R. Potter. *J. Biol. Chem.* 209: 41, 1954.
183. Shepherd, J. A. and G. Kalnitsky. *J. Biol. Chem.* 207: 605, 1954.
184. Sloane-Stanley, G. H. *Biochem. J.* 49: iv, 1951.
185. Sloane-Stanley, G. H. *Biochem. Soc. Sympos.* 8: 44, 1952.
186. Sloane-Stanley, G. H. *Biochem. J.* 53: 613, 1953.
187. Smallman, B. N. *J. Physiol.* 132: 343, 1956.
188. Solomon, A. K., F. Lionetti and P. F. Curran. *Nature, London* 178: 582, 1956.
189. Sperry, W. M. *J. Biol. Chem.* 170: 675, 1947.
190. Stadie, W. C. and B. C. Riggs. *J. Biol. Chem.* 154: 687, 1944.
191. Stern, J. R., L. V. Eggleston, R. Hems and H. A. Krebs. *Biochem. J.* 44: 410, 1949.
192. Stern, J., H. Weil-Malherbe and R. H. Green. *Biochem. J.* 52: 119, 1952.
193. Stone, D. and S. Shapiro. *Am. J. Physiol.* 155: 141, 1948.
194. Stone, W. E. *Meth. med. Res.* 1: 353, 1948.
195. Strecker, H. J., P. Mela and H. Waelsch. *J. Biol. Chem.* 212: 223, 1955.
196. Strickland, K. P. *Canad. J. Med. Sci.* 30: 484, 1952.
197. Strickland, K. P. *Canad. J. Biochem. & Physiol.* 32: 50, 1954.
198. Strickland, K. P. and R. H. S. Thompson. *Biochem. J.* 60: 468, 1955.
199. Strickland, K. P., R. H. S. Thompson and G. R. Webster. *Biochem. J.* 62: 572, 1956.
200. Strominger, J. L. and O. H. Lowry. *J. Biol. Chem.* 213: 635, 1955.
201. Svennerholm, L. *Acta Chem. Scand.* 10: 694, 1956.
202. Svennerholm, L. *J. Neurochem.* 1: 42, 1956.
203. Taylor, J. D., R. K. Richards, G. M. Everett and E. L. Bertcher. *J. Pharmacol.* 98: 392, 1950.
204. Terner, C., L. V. Eggleston and H. A. Krebs. *Biochem. J.* 47: 139, 1950.
205. Thannhauser, S. J. and M. Reichel. *J. Biol. Chem.* 113: 311, 1936.
206. Thomas, J. *Biochem. J.* 64: 335, 1956.
207. Thomas, J. *Biochem. J.* 65: 8p, 1957.
208. Thomas, J. and H. McIlwain. *J. Neurochem.* 1: 1, 1956.
209. Tower, D. B. *Neurology* 5: 113, 1955.
210. Tower, D. B. In: *Progress in Neurobiology. I. Neurochemistry*, edited by S. Korey and J. I. Nurnberger. London: Cassell, 1956, p. 169.
211. Tyrrell, L. W. *Nature, London* 166: 310, 1950.
212. Utter, M. F. *J. Biol. Chem.* 185: 499, 1950.
213. von Muralt, A. *Die Signalübermittlung im Nerven.* Basle: Birkhauser, 1946.
214. Waelsch, H. *Advances Protein Chem.* 6: 299, 1951.
215. Waelsch, H. (editor). *Biochemistry of the Developing Nervous System.* New York: Acad. Press, 1955.
216. Weil-Malherbe, H. *Biochem. J.* 30: 665, 1936.
217. Weil-Malherbe, H. *Biochem. J.* 31: 308, 1937.
218. Weil-Malherbe, H. *Biochem. J.* 32: 2287, 1938.
219. Weil-Malherbe, H. *Physiol. Rev.* 30: 549, 1950.
220. Weil-Malherbe, H. *Biochem. Soc. Sympos.* 8: 16, 1952.
221. Weil-Malherbe, H. and A. D. Bone. *Biochem. J.* 49: 339, 1951.
222. Weil-Malherbe, H. and R. H. Green. *Biochem. J.* 61: 210, 1955.
223. Weil-Malherbe, H. and R. H. Green. *Biochem. J.* 61: 218, 1955.
224. Williams, R. T. (editor). *Biochem. Soc. Sympos.* 8: 3, 1952.
225. Witter, R. F. *Canad. J. Biochem. & Physiol.* 34: 332, 1956.
226. Wollemann, M. and G. Feuer. *Acta Physiol. Acad. Sci. Hung.* 7: 329, 1955.
227. Wollenberger, A. *Biochem. J.* 61: 77, 1955.
228. Ziegler, D. M. and J. B. Melchior. *J. Biol. Chem.* 222: 721, 731, 1956.

CHAPTER LXXVII

# Metabolism of the central nervous system in vivo

LOUIS SOKOLOFF | *National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland*

CHAPTER CONTENTS



AN UNDERSTANDING of the normal patterns of metabolism and their relation to function is in the case of the central nervous system probably more dependent on the results of *in vivo* studies than in any other system of the body. Because of its role as a communications system, the functioning of the central nervous system is completely integrated with the various activities going on within its own various parts, in other parts of the nervous system and in almost all other structures of the body. Furthermore, the major portion of the central nervous system, the brain, is involved in the unique processes which subserve the phenomenon of consciousness. It is impossible to conceive of either of these functions, communications or consciousness, and their supportive metabolic processes operating under the isolated conditions required by *in vitro* experiments.

Furthermore, certain unique features of the metabolism of the central nervous system amplify the importance of *in vivo* studies. Its normal functions are completely dependent on the obligatory consumption of oxygen and glucose, and its metabolic rate is normally very great, particularly in relation to its stores of these essential nutrients. It is, therefore, dependent on a continuously adequate renewal of these nutrient materials by means of a relatively enormous blood flow, approximately 55 ml per 100 gm per min., and interruption of these supplies rapidly leads to impairment of function and irrevers-

ible changes. In these circumstances, metabolism does not cease. The metabolic rate is slowed, but chemical processes, obviously abnormal since they lead to irreversible functional changes, persist. *In vitro* studies, in which tissue blood flow is necessarily nonexistent, are particularly susceptible to the appearance of such artifactual chemical processes.

An additional peculiarity of the central nervous system which operates only in the normal *in situ* state is the so-called blood-brain barrier. Metabolites capable of being utilized by the tissues of the nervous system, as indicated by *in vitro* studies, cannot penetrate into these tissues from the blood because of the selective permeability of this barrier. In *in vitro* studies the blood-brain barrier is bypassed so that the results indicate only the potential capabilities of the enzymatic systems within the tissues of the central nervous system. It remains for *in vivo* studies to determine which of these capabilities are fulfilled in the actual functional state. It is, therefore, indeed fortunate that there are available *in vivo* methods which are not only adequate, at least in regard to the brain, but are also applicable to studies in conscious unanesthetized man.

## METHODS

Several techniques have been employed to study the metabolism of the central nervous system *in vivo*. These vary considerably in complexity and in the degree to which they yield quantitative results. Some require such minimal operative procedures on the experimental animal that no anesthesia is necessary, and little or no interference with the tissue occurs except for the effects of the experimental condition under study. Others involve such extensive surgical intervention that the experiment approaches an *in vitro* study *in situ*.

### *Simple Behavioral-Chemical Correlation Techniques*

The earliest and least complex of the techniques for studying central nervous system metabolism *in vivo* has been, perhaps, simply the observation of the effects on the behavior of the animal of administering chemical agents into the blood or spinal fluid. A more refined variant of this technique is the correlation between blood or spinal fluid levels of chemical substances or metabolites and behavior. It is precisely by such techniques, for example the effect of insulin administration on blood glucose levels and consciousness and the restorative action of glucose, that the vital role of glucose in the cerebral metabolism was discovered (20, 122).

Other, more objective criteria have been employed as indicators of the effects of the chemical substances studied. Changes in electroencephalographic patterns, electrical responses or reflex functions have thus been employed (16, 24, 81, 85, 190), the latter two being particularly useful for studies on the spinal cord in which functional changes are less manifested by distinct behavioral alterations.

The chief virtues of this group of methods are their simplicity and their applicability under conditions closely approximating the physiological state. They are, however, gross and nonspecific, and do not always distinguish between a direct effect of the experimental agent on the metabolism of the nervous system and one secondary to changes produced in somatic tissues. Similarly, negative results are often inconclusive, for there always remains the possibility of insufficient dosage, inadequate circulation or the impermeability of the blood-brain barrier.

### *Tissue Content and Incorporation Techniques*

The availability of suitable chemical analytical techniques makes possible quantitative analysis of central nervous tissue for specific metabolites at given times during control periods or during or after exposure of the animal to experimental conditions. Although such methods require sacrifice of the animal, they are in reality *in vivo* methods since they determine the state of the tissue while still in the animal. For example, by such an approach the effects of various conditions such as anesthesia or convulsions on the adenosine triphosphate level of brain tissue (136, 182, 183), or the effects of insulin hypoglycemia on brain carbohydrate stores (90) have been determined.

The development of radioactive tracer techniques has added much to the usefulness of these methods (26). The determination of the rate of incorporation of radioactive compounds from the blood or spinal fluid into the tissues of the central nervous system leads to quantitative data on the penetrability of the blood-brain barrier by the test substance as well as its half-life or turnover rate in the tissues. Similarly, the incorporation of a radioisotope of the administered compound into its metabolic products serves not only to identify the intermediate pathways of metabolism but also to quantify the rates of synthesis and turnover of the metabolites derived from the test sub-

stance in the tissues of the nervous system. For example, $C^{14}$-labeled lysine has been thus employed in mice to determine the half life of free lysine and lysine-containing proteins of the brain (107). A similar approach has been used to study the effects of pentobarbital anesthesia, electrically induced convulsions and insulin hypoglycemia on the rate of incorporation of radioactive phosphorus ($P^{32}$), administered as phosphate, into the phospholipids and nucleoproteins of the mouse brain (28).

This group of methods, particularly those utilizing radioisotope tracer techniques, is a valuable addition to the armamentarium for studying central nervous system metabolism *in vivo*. They permit under more or less physiological conditions quantitative investigations of the intermediary metabolism not presently possible by any other *in vivo* techniques. On the other hand, they are subject to the usual restrictions imposed by the blood-brain barrier; they are, therefore, limited to materials which can penetrate into the nervous tissues from the blood or, in some cases, the spinal fluid. They require reliable data on the content of the blood within the tissue studied so that proper correction for the contribution by the blood to the quantity of radioactivity or metabolite, or both, found in the tissue can be made. Finally, they require the sacrifice of the animal for each experiment.

*Arteriovenous Differences*

Substances exchanged between central nervous system tissues and blood are present in different concentrations in arterial and venous bloods. For a steady state of blood flow, the arteriovenous difference is directly proportional to the rate of utilization or production of the metabolite by the tissue.

This technique has been the basis of some of the earliest studies of cerebral metabolism in man (20, 116, 117) in whom it can be employed without anesthesia and where, because of a favorable vascular anatomy, it is most readily applicable. Arterial blood can be obtained from any artery, but the venous blood presents special problems. It must be representative of the mixed venous drainage of the tissue under study; otherwise, it represents undefined areas of that tissue. It must also be relatively uncontaminated by blood from tissues other than the one under study. These requirements are satisfactorily achieved in man by sampling of cerebral venous blood from the superior bulb of the internal jugular vein by the technique of Myerson *et al.* (133). Blood thus drawn is representative of the brain as a whole and contains only three per cent contamination from extracerebral sources (168). In the common laboratory animals, except for the monkey, the anatomy of the cerebral circulation is such that extensive communications between cerebral and extracerebral venous blood occurs (7). It is, therefore, generally difficult without major surgical intervention to obtain suitable representative cerebral venous blood samples. Such studies have, however, been carried out in lower animals, but they are usually of questionable specificity.

The advantage of this method lies in its relative simplicity and its applicability to unanesthetized man. Since arteriovenous differences depend not only on metabolic rate but on blood flow as well, they do not yield quantitative data on rates of utilization or production. They do, however, give information on the direction and relative rates of utilization or production of those metabolites which pass the blood-brain barrier. Moreover, comparisons of rates of utilization or production among various metabolites are possible, as, for example, the comparison of the oxygen and carbon dioxide arteriovenous differences in the determination of the cerebral respiratory quotient *in vivo*.

*Combination of Blood Flow and Arteriovenous Differences*

By combining the measurment of blood flow with the determination of arteriovenous concentration differences, the rates of utilization or production of specific metabolites can be quantitatively estimated. These rates are simply the products of the values for blood flow and arteriovenous difference. The methods for the measurement of blood flow in the central nervous system have for the most part been applicable only to the brain, and even here most of them are open to serious criticism (66). (They are discussed by Kety in Chapter LXXI of this *Handbook*.)

Perfusion methods have been employed in studies on the entire head (15), the whole isolated brain (18, 51), portions of the cerebral cortex (67) and parts of the spinal cord (190), sometimes in association with a flow-meter device to measure the rate of flow of the perfusate, or of blood during natural perfusion of the brain by the animal's own circulation. These devices include the rotameter (66, 150), thermoelectric devices (57, 66) and the bubble-flow meter (31, 66). One of these, the thermoelectric flow recorder (57), is designed in the form of a needle which when inserted into the jugular vein of man has been capable of yielding relative values for human

cerebral blood flow. In general, perfusion methods and flow-meter techniques are limited by their requirement of extensive operative procedures, particularly in most laboratory animals in which the anatomy of the cerebral vasculature is unsuitable (7).

In man, plethysmographic techniques (45) and dilution techniques employing either T-1824 (Evans blue dye) (58, 91) or thorium B-labeled red cells (134) have been employed for quantitative measurement of human cerebral blood flow, but the nitrous oxide method of Kety & Schmidt (91, 100) has been most widely used and found to yield the most reliable results. (A description of the details of these methods and their critical evaluation are presented by Kety in Chapter LXXI of this *Handbook*.) The original nitrous oxide method has been adapted for use in animals (106, 137), and several modifications have been employed in man. One simplifies it and reduces the volume of blood sampling required by the procedure (158). Another adapts it to children (87, 88), and a third substitutes the radioactive gas, $Kr^{85}$, for nitrous oxide as the tracer material with some improvement in the precision of the method (114).

### *Polarographic Techniques*

The oxygen electrode has been employed for the *in vivo* measurement of local cortical oxygen tension and consumption (22, 23). By applying such an electrode to the surface of the exposed cortex, one can make continuous measurements of cortical oxygen tension before and during occlusion of the circulation to the local area. During occlusion the oxygen tension falls linearly as oxygen is consumed by the tissue, and the rate of fall is a measure of the local cortical oxygen consumption. This technique has also been employed in combination with the artificial perfusion of an isolated section of cerebral cortex (67).

## CHARACTERISTICS OF NORMAL METABOLISM OF THE CENTRAL NERVOUS SYSTEM IN VIVO

Almost all of our present knowledge concerning the substances normally utilized and produced by the metabolism of the central nervous system is derived from studies of the brain, frequently made in human subjects, both normal and pathological.

In table 1 are summarized the reported results of such studies in normal adult human subjects. The range of the mean values reported by the various investigators is presented; and since the techniques, the degree of precision, and the nature and number of the subject material vary somewhat from one laboratory to another, the median of the mean values was chosen as most representative of the function studied.

### *Normal Substrates and Products*

The functions presented in table 1 are the arterial-cerebral venous differences for various metabolites

TABLE 1. *Substances Utilized or Produced by Normal Young Adult Human Brain*

| Substances | Arteriovenous Difference per 100 ml Blood | | Metabolic Rates per 100 gm Brain per min. | | References |
|---|---|---|---|---|---|
| | Range* | Median* | Range* | Median* | |
| Substances utilized | | | | | |
| Oxygen | +5.9 to +6.9 vol.% | +6.4 vol.% | +3.3 to +3.9 ml | +3.5 ml | 12, 56, 95, 100, 108, 114, 121, 158, 178, 198 |
| Glucose | +9.0 to +9.9 mg% | +9.0 mg% | +4.9 to +6.2 mg | +5.5 mg | 56, 95, 158, 178, 198 |
| Glutamic acid | | +0.78 mg% | | +0.4 mg | 1 |
| Substances produced | | | | | |
| Carbon dioxide | −5.6 to −6.6 vol.% | −6.3 vol.% | −3.1 to −3.7 ml | −3.5 ml | 12, 56, 108, 121, 178, 198 |
| Glutamine | | −1.26 mg% | | −0.6 mg | 1 |
| Substances studied with insignificant utilization or production | | | | | |
| Lactic acid | −1.6 to +3.0 mg%† | −0.04 mg%† | | | 56, 95, 198 |
| Pyruvic acid | | +0.11 mg%‡ | | | 95 |
| α-Ketoglutarate | | +0.04 mg%‡ | | | 95 |
| Total ketones | | −0.04 mg%‡ | | | 95 |

* Mean values reported by various authors.

† Two of three reported means statistically significant ($p < 0.05$) but of opposite signs.

‡ Not statistically significant from zero ($p > 0.05$).

and their rates of utilization or production per 100 gm of average brain taken as a whole per minute, derived from studies employing the nitrous oxide technique under more or less physiological conditions.

It is apparent from table 1 that the ultimate source of energy for the brain under normal conditions is the oxidation of glucose. The only energy-yielding substances shown consistently and repeatedly to be removed from the blood in significant amounts by the brain are oxygen and glucose, and the only product of the cerebral metabolism, other than water, consistently released to the blood is carbon dioxide. The finding of an uptake by the normal brain of glutamic acid with a release of glutamine by Adams and his co-workers (1) requires further confirmation, particularly in view of the observation in mice and rats by Schwerin *et al.* (164) of the inability of glutamic acid to penetrate the blood-brain barrier. At any rate, the uptake of glutamic acid is exactly balanced by the release of glutamine, indicating a combination of glutamate with ammonia, a process requiring rather than liberating energy. The role of this reaction may be simply the detoxification of ammonia released during cerebral functional activity (25, 141, 143).

Of the other substances studied, no significant utilization or production by the brain of $\alpha$-ketoglutarate or ketone bodies, such as acetoacetate or $\beta$-hydroxybutyrate, has been observed in normal human subjects and patients in diabetic acidosis (95) or in ketotic animals (131). As for pyruvate and lactate, the results have been inconsistent. In normal human subjects two studies have reported significant arterial-cerebral venous lactate differences, one indicating uptake (198) and the other release (56) by the brain. Kety (95) has found no evidence of lactate or pyruvate utilization or production in normal human subjects, and no pyruvate but definite lactate production in diabetic acidosis. Himwich & Himwich (82) have observed a small but significant production of both lactate and pyruvate in a group of hospital patients. It is likely that there is normally a small production of lactate and pyruvate by the brain, but that the present analytical methods are not sufficiently precise to detect it consistently. During cerebral anoxia, however, the release of lactate has been found in animals to be considerable and easily demonstrated (128).

Recently Martin and co-workers (124) have demonstrated in rabbits that, although total glutathione concentration is unchanged in the blood passing through the brain, 30 per cent of the reduced glutathione is converted to the oxidized form. The arteriovenous differences for both the reduced and oxidized forms of glutathione are, therefore, considerable on a weight basis, approximately 7.5 mg per cent or two thirds that of glucose; but this oxidation accounts for only $\frac{1}{41}$ of the total oxygen consumption of the brain. Preliminary observations in normal human subjects indicate a similar phenomenon (McIlwain, personal communication). The significance of this reaction to cerebral metabolism and function is at present unknown.

The failure to demonstrate significant arteriovenous differences for other metabolites does not preclude a role for them in the cerebral metabolism. Their rates of utilization or production by the brain may be so small that their arteriovenous differences are rendered insignificant by the normally rapid cerebral blood flow. For example, radioactive tracer studies with $C^{14}$-labeled lysine (107) have demonstrated its rapid incorporation from the blood into the proteins of the mouse brain, despite an insignificant arteriovenous difference. Metabolites may be unable to traverse the blood-brain barrier, but when administered directly into the spinal fluid, are taken up by the brain. Thus, $S^{35}$-methionine has been found to be incorporated into brain proteins from spinal fluid but not from blood (49). Such substances, although not supplied exogenously by the blood, may be formed endogenously within the brain by the cerebral metabolism and utilized there to a considerable degree. *In vitro* studies, for example, have demonstrated the ability of cerebral tissues to metabolize a number of intermediates of the glycolytic and tricarboxylic cycles which do not exchange between brain and blood (19).

### *Normal Metabolic Rate*

From the data on the rate of oxygen consumption of the brain presented in table 1, it is apparent that its energy output is quite substantial, indeed one of the highest of all the organs of the body. Consuming oxygen at an average rate of 3.5 ml per 100 gm per min., a brain of average weight, approximately 1,400 gm, accounts for a total oxygen consumption of 49 ml per min. or almost 20 per cent of the total basal body oxygen consumption of the normal young human adult. Kennedy and his associates (87) have found even higher cerebral metabolic rates in childhood (fig. 1), approximately 40 per cent higher, so that in a 5-year old child, for example, the brain, which at this age has reached close to its mature size, may consume half of the total body oxygen uptake.

The rapid rate of cerebral oxygen consumption is almost balanced by the carbon dioxide production

so that the cerebral respiratory quotient is 0.97 or approximately unity (tables 1 and 2). In neither man nor animals have any significant differences from this value been observed, even during severe metabolic disorders such as hypoglycemia (103), diabetic acidosis (99), or ketosis arising from starvation or fat feeding (131).

Comparison of the oxygen and glucose arteriovenous differences reveals one of the unique features of the cerebral metabolism. As shown in table 2, the oxygen and glucose consumptions are 156 and 31 μmole per 100 gm per min., respectively. Since 6 moles of oxygen are required for the complete oxidation of 1 mole of glucose, the rate of cerebral oxygen consumption is equivalent to only 26 μmole of glucose per 100 gm per min. Five μmole per 100 gm per min., or about 16 per cent of the total glucose consumption, remain unoxidized. However, the actual discrepancy from complete stoichiometric equivalence is small and can, perhaps, be the result of systematic errors in the analyses for oxygen and glucose, particularly the latter since the analytical methods employed in its determination have not been specific and have included other reducing substances in the blood. An alternative explanation is that of Himwich & Himwich (82) who in their studies found the cerebral lactate and pyruvate production to be approximately equivalent to the excess glucose not accounted for by the oxygen consumption. A third possibility to be considered is simply that this additional glucose taken up by the brain is utilized not for the production of energy but for the synthesis of other chemical constituents of the brain.

The combination of a cerebral respiratory quotient approximating one, an almost stoichiometric relationship between the oxygen and glucose uptakes for the complete oxidation of the latter, and the absence of any significant arteriovenous difference for any other energy-rich substrate is strong evidence that the brain derives its energy for normal functions almost exclusively from the oxidation of glucose. In this respect the cerebral metabolism is quite unique in that no other tissue, except possibly the testes (84), has been found to rely for energy on carbohydrate alone. On the other hand, this does not imply that the pathways of glucose metabolism in the brain lead directly only to oxidation. Various chemical and energy transformations between the initial energy sources, oxygen and glucose, and the final products, carbon dioxide and water, may occur so that various intermediate compounds derived from glucose or produced by the energy made available from glucose

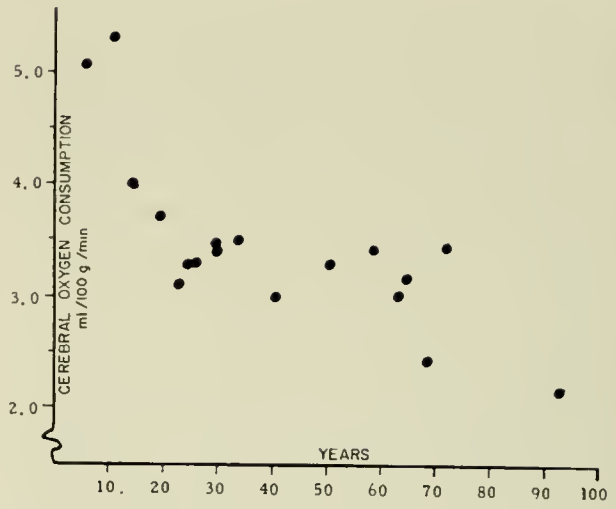



FIG. 1. Changes in normal human cerebral oxygen consumption with age. [Modified from Kety (93, 94). Includes data from following references: 37, 43, 87, 88, 100, 121, 132, 157, 158, 161, 169, 175, 179; Sokoloff, Dastur, Lane & Kety, unpublished observations.]

catabolism may be the actual substances finally oxidized. Indeed, Sacks (152) in studies with $C^{14}$-labeled glucose in human beings obtained results suggesting the production of carbon dioxide by the brain from sources other than glucose. The fact remains, however, that so long as the oxygen and glucose utilization and carbon dioxide production are in such complete balance and no other energy-laden substrate is taken from the blood, then the net energy made available to the brain must ultimately be derived from the oxidation of glucose.

The rates of cerebral metabolism presented here are average values for the brain taken as a whole. Although no reliable quantitative data on the metabolic rates *in vivo* of the various component structures of the brain are available, it is likely that there is considerable heterogeneity in this respect. Quantitative studies of local cerebral blood flow, which in the normal state probably correlates well with local cerebral metabolic rate, indicate considerable differences among the various cerebral structures. In the brain of the conscious cat, Kety and his associates (97, 109, 176) have found the blood flow of gray structures to be approximately five times that of white matter; and of the gray structures the inferior colliculus had the highest rate, followed by the primary sensory areas of the cortex. It is likely that the distribution of metabolic rates is similar.

TABLE 2. *Relationship between Oxygen and Glucose Metabolism in Normal Young Adult Human Brain*

| | Range of Mean Values | Median of Mean Values | References |
|---|---|---|---|
| Cerebral respiratory quotient | 0.92 to 0.99 | 0.97 | 12, 56, 100, 108, 121, 178 |
| Oxygen/glucose ratio (mmole/mmole) | 4.9 to 6.2 | 5.5 | 56, 95, 158, 178, 198 |
| Oxygen consumption (μmole/100 gm/min.) | | 156* | (see table 1) |
| $CO_2$ production (μmole/100 gm/min.) | | 156* | (see table 1) |
| Glucose consumption (μmole/100 gm/min.) | | 31* | (see table 1) |
| Totally oxidized glucose accounted for by oxygen consumption (μmole/100 gm/min.) | | 26† | |

* Calculated from median values reported in table 1.

† Calculated on basis of 6 moles of oxygen required for complete oxidation of 1 mole of glucose.

*Evidence for Obligatory Aerobic Utilization of Glucose by the Central Nervous System*

The fact that the central nervous system under normal circumstances derives its energy from the oxidation of glucose does not reveal the entire picture of the uniqueness of its metabolism. In the normal state when all possible substrates are available, it may simply reflect the preferential metabolic pathways. However, the available evidence at present strongly indicates that the aerobic utilization of glucose is not a preferential pathway but an obligatory one for the maintenance of normal function. The available stores of oxygen and glucose within the central nervous tissues are so small compared with their rate of consumption that the functions of the nervous system are completely dependent on their constant uninterrupted renewal by the circulation. Complete cessation of the cerebral circulation in man, for example, results in the loss of consciousness within 10 sec. (151), the approximate interval of time required to utilize the estimated stores of oxygen within the brain (92). Since the stores of glucose and glycogen within the brain are relatively greater than that of oxygen (89, 90, 92), the acuteness of this effect is almost certainly the result of a deficiency of oxygen rather than of glucose. Furthermore, the well-known effects of anoxia or anoxemia on cerebral functions leave little doubt of the essential nature of oxidative metabolism for the maintenance of these functions. (These effects are discussed also by Tschirgi in the subsequent chapter in this volume.)

The evidence that normal function in the nervous system is dependent upon the obligatory consumption of glucose is derived mainly from three groups of *in vivo* observations.

IMPAIRMENT OF CENTRAL NERVOUS SYSTEM ACTIVITY PRODUCED BY GLUCOSE DEPRIVATION. It is well known that in man a fall in blood glucose concentration is associated with changes in mental state ranging from mild subjective sensory disturbances to coma. (See also Tschirgi's account of hypoglycemic effects in the following chapter in this volume.) The degree of functional or behavioral impairment is well correlated with the degree of hypoglycemia (20, 81, 103, 118, 122). Abnormalities in the electroencephalogram, for example increasing prominence of delta rhythms (16, 24, 81, 85) and reductions in the cerebral arteriovenous oxygen difference (75, 76, 78, 80, 103, 198) and oxygen consumption (103), increase with decreasing blood glucose levels. According to Kety and co-workers (103), when the arterial blood glucose level was reduced from a normal level of 70 to 100 mg per cent to a mean value of 19 mg per cent, schizophrenic patients given insulin became confused and the mean cerebral oxygen consumption fell to 2.6 ml per 100 gm per min. or 79 per cent of the normal level. At an arterial glucose level of 8 mg per cent, deep coma ensued and cerebral oxygen consumption decreased further to 1.9 ml $O_2$ per 100 gm per min. These changes occurred despite a slight increase in cerebral blood flow. In the state of coma the cerebral glucose utilization was negligible, 0.8 mg per 100 gm per min. Animals exhibit similar behavioral and electroencephalographic changes during hypoglycemia (120, 123). Although in most of the reported studies hypoglycemia was produced by insulin administration, the described changes cannot at present be attributed to a direct action of insulin on the central nervous system. First, the degree of altered function is correlated with the degree of hypoglycemia and not the insulin dosage. Secondly, the admin-

istration of glucose either simultaneously or after the administration of insulin prevents or alleviates the effects. Thirdly, the same effects are observed in hypoglycemia resulting from hepatectomy (120, 123), and also after the blockage of normal glucose utilization by administration of apparently a competitive inhibitor, 2-desoxyglucose, despite the elevation in the blood glucose level produced (Morrell & Landau, personal communication).

On the other hand, perfusion experiments in isolated tissues have led to contradictory results. In the isolated thoracic spinal cord of the rat, Tschirgi and associates (190) have observed the abolition of reflex responses during glucose-free perfusion but their recovery on restoration of glucose to the perfusate. Grenell & Davies (67), however, have observed no effect of glucose deprivation on the spontaneous electrical activity or oxygen consumption of a perfused segment of cerebral cortex maintained *in vivo* in the cat. Grenell & Wolbarsht (69) have found evidence suggesting that the cortical electrical changes produced by insulin are secondary to a direct action of that agent on subcortical structures. Geiger and co-workers (52) have found in the cat brain that during glucose-free perfusion convulsive activity can occur with the same acceleration of oxygen consumption as when glucose is present. In fact, even when glucose is present in the perfusate, the increased carbohydrate breakdown which then occurs in the brain during convulsions does not require the added oxygen consumed, for it can be entirely accounted for by the increased lactic acid production. They interpret these results as indicative of the existence of noncarbohydrate materials in the brain which are oxidized and account for the increased oxygen consumption during convulsions. In previous studies on the same preparation, Geiger and his associates (53) have demonstrated a fall in cerebral oxygen consumption when fructose was substituted for glucose in the perfusate. Fructose disappearance within the brain began only after glucose had disappeared from the tissues, and then the oxygen consumption was greater than could be accounted for by fructose utilization alone. The additional oxygen was believed to be consumed in the oxidation of glutamate and glutamine in the cortex.

The results of the perfusion experiments are difficult to evaluate inasmuch as they are performed in preparations which can hardly be considered to be demonstrating normal functions. Furthermore, the experiments in the perfused cat brain must always be carefully scrutinized for errors arising from the inherent difficulties in isolating the cerebral from the extracerebral circulations. At best these studies have demonstrated that the brain is capable of oxidizing substances other than glucose, but it is not oxygen consumption which is believed to be dependent on glucose utilization. Even in man in hypoglycemic coma, cerebral oxygen consumption, although reduced, goes on despite negligible glucose utilization (103). It is the normal functioning of the central nervous system which requires the oxidation of glucose, and perfused cerebral tissues are hardly adequate to test this relationship.

RECOVERY FROM EFFECTS OF HYPOGLYCEMIA PRODUCED BY GLUCOSE ADMINISTRATION. The administration of glucose during the period of altered functions produced by hypoglycemia rapidly restores these functions to normal. In man in insulin coma such restoration can occur within a few minutes (98). Similarly, the simultaneous administration of glucose can prevent the development of hypoglycemia and its effects by insulin.

RELATIVE INABILITY OF OTHER SUBSTRATES TO PRODUCE RECOVERY FROM EFFECTS OF HYPOGLYCEMIA. In hepatectomized animals, the effects of hypoglycemia on behavior or cortical electrical activity, or both, are not counteracted by lactose, inulin, fructose, galactose, hexosediphosphate, ethanol, glyceraldehyde, lactate, pyruvate, acetate, succinate, fumarate or glutamate (120, 123). Mannose and maltose have been found to restore in these preparations both normal behavior and electroencephalographic activity, but their effectiveness is believed to be the result of their prior conversion to glucose (120, 123). In the isolated perfused thoracic spinal cord of the rat, Tschirgi and associates (190) have found that the reflex responses which are eliminated by glucose deprivation are restored fully by pyruvate, isocitrate, glutamine, $\alpha$-ketoglutarate and glutamate. The effects of the latter two were associated with the appearance of glucose in the perfusate, but in the case of the others there was no obvious reason to suspect any conversion to glucose. In the same preparation oxaloacetate partially restored function; alcohol, acetate, lactate, $\beta$-hydroxybutyrate, fumarate, malate, succinate, epinephrine, DL-alanine, DL-lysine, L-tyrosine, DL-aspartate, DL-cysteine and L-cystine were without effect, although some of them were readily oxidized. In insulin coma in man, lactate (76, 199), pyruvate (60, 76) and ethanol (59) have been ineffective for restoring consciousness. Mayer-Gross &

Walker (125) found that glutamate, aminoacetate and paraminobenzoic acid would occasionally restore conscious behavior in man during insulin coma but that they also caused an elevation in blood glucose level. Succinate was found to do neither. Weil-Malherbe (195) has occasionally found glutamate, arginine, glycine and succinic acid to produce arousal from insulin coma, but this effectiveness was believed to result from an increased blood glucose concentration secondary to the elevation in blood epinephrine level caused by these substances.

It is clear that few substances other than glucose can reverse the effects of hypoglycemia in man, and in those cases it is likely that they do so by increasing the blood glucose concentration. On the other hand, the failure of a substance to restore normal functions during hypoglycemia may be the result of inadequate dosage or an inability to penetrate the blood-brain barrier. It does not prove its inability to substitute for glucose once it is in the tissues in adequate amounts. However, as regards the functioning of the nervous system of the intact animal, which is dependent on substrates supplied only by the blood, no adequate substitute for glucose has been found, and it must, therefore, be considered essential for normal physiological behavior of the central nervous system.

### *Miscellaneous Substances of Importance in Metabolism of the Central Nervous System*

Recent developments have led to an increased interest in the many substances other than glucose and oxygen that must be of vital importance in the metabolic functions of the central nervous system. Oxygen and glucose are concerned only with the production of available energy, but there are innumerable substances and processes involved in the transfer and utilization of this energy. Studies involving the chemical analysis of brain tissue obtained from animals exposed to various experimental conditions indicate, for example, that phosphates and nucleotides play the same role in the transfer of energy within the brain as in other tissues (129). During periods of reduced cerebral activity, such as sleep or narcosis, energy-rich phosphate compounds accumulate (141), and during increased activity, such as convulsions, they are depleted and inorganic phosphate is increased (141). Nitrogen-containing compounds have also been implicated in the metabolic processes associated with activity of the central nervous system. During increased nervous activity there is an increase of nonprotein nitrogen and ammonia within the brain (52, 194). It is likely that the reactions involving the reductive amination of ketoglutarate to form glutamate and the amidation of glutamate to form glutamine are of fundamental importance in the ammonia metabolism of the brain (14, 194).

Recently, γ-aminobutyric acid, formed by the decarboxylation of glutamate by an enzyme more concentrated in the central nervous system than in other tissues (4, 146–148, 197), has been suspected of being a chemical mediator of central inhibition (10, 32, 71). Since pyridoxal-5′-phosphate is an essential coenzyme in this reaction, a major role for pyridoxine in the metabolism and function of the central nervous system is evident (148, 149, 191). Indeed, the production of convulsive states by pyridoxine deficiency or antagonists has already suggested such a role (186).

In studies in the perfused cat brain, Geiger and his associates have found that the very ability of the brain to maintain both aerobic utilization of glucose and function is dependent upon the availability of the two pyrimidine nucleosides, cytidine and uridine (54). In their absence, impermeability to glucose and depletion of brain galactoside and phospholipid contents developed. Uridine alone restored the galactoside contents and cytidine the phospholipid contents to the normal level. Both were needed for the restoration of normal carbohydrate metabolism and function.

It is evident then that there is a vast array of metabolic processes not directly related to the aerobic utilization of glucose but vitally concerned with the functional activity of the tissues. However, many of these reactions require energy and are thus dependent on the oxidation of glucose for this energy. Similarly, the ability of the central nervous system to provide energy by the oxidation of glucose is in turn dependent on the maintenance of the integrity of these other metabolic processes.

## PHYSIOLOGICAL INTERRELATIONSHIPS OF METABOLISM OF THE CENTRAL NERVOUS SYSTEM

There have been no convincing studies to date to indicate any qualitative changes in the nature of the metabolism of the central nervous system with changing physiological states. Any changes, such as they are, have been mainly in rate and even then, compared with other organs, the metabolic rate of the central nervous system, at least the brain as a whole, appears to vary so little as to suggest that it possesses

a considerable degree of autonomy. However, it is of interest to examine the relationship of the small degree of variability of cerebral metabolism to its own physiological state and that of the rest of the body.

*Relationship of Cerebral Metabolism to Circulation*

As is true in all tissues, the purpose of the cerebral circulation is to supply the brain with essential nutrients and to remove the products of its metabolism. As long as blood flow is adequate to perform these functions, it has no influence on the metabolic rate. Under normal conditions, metabolic rate is never limited by the blood flow, and increasing the blood flow does not alter that rate (92, 101). The rates of exchange of metabolites between brain and blood remain the same; the arteriovenous differences merely decrease in proportion to the increase in blood flow. When blood flow is reduced in the presence of a constant metabolic demand, the reverse occurs, and the arteriovenous differences increase proportionately until a limit is reached beyond which the brain no longer is able to extract adequate amounts of nutrient material to support its metabolic needs. This limit is quite low as indicated by the studies of Finnerty and co-workers (46) who found that cerebral blood flow could be reduced by drug-induced arterial hypotension to approximately 60 per cent of the normal value or to the point of fainting without any measurable decrease in the cerebral oxygen consumption. Eventually, however, the cerebral metabolic rate can be reduced by a deficient circulation as in secondary shock (42) or in conditions of markedly increased intracranial pressure (102), sometimes to a level so low that unconsciousness ensues. It is only under such conditions that raising the rate of blood flow increases the metabolic rate. When such a phenomenon occurs, it is pathognomonic of tissue ischemia, and any experimental preparation in which it occurs, as for example the perfused cat brain employed by Geiger and co-workers (51), must be suspected of this serious defect.

Although cerebral metabolic rate can be maintained independent of the blood flow over a wide range, in normal circumstances it is probably not exposed to extremes of blood flow. Homeostatic mechanisms exist which adjust the cerebral blood flow to the metabolic demands and so to the functional activity of the brain. The mechanisms achieving this regulation are discussed by Schmidt in Chapter LXX and by Kety in Chapter LXXI in this *Handbook*.

*Relationship of Cerebral Metabolism to Growth, Development and Age*

In figure 1 is presented a modification of the graph constructed by Kety (93, 94) from the data obtained in various laboratories illustrating the effect of aging on the rate of cerebral oxygen consumption in normal man. The modification consists of the inclusion of data from two recently reported studies (132, 175; Sokoloff, Dastur, Lane & Kety, unpublished observations). It is seen from figure 1 that cerebral metabolic rate in normal subjects is high in childhood, presumably during growth and development of the brain, decreases most rapidly until puberty or mid-adolescence, falls more slowly between puberty and early adulthood, and then remains relatively constant thereafter into senescence. The previous belief that cerebral metabolic rate normally falls progressively throughout the life span arose from inclusion in the older groups of patients with various vascular and nervous diseases commonly associated with aging in which cerebral oxygen consumption has been found to be reduced (41, 48, 115, 169). This is probably the reason for the obvious disparity of the two lowest points in figure 1 which were obtained in hospital patients not as rigorously screened for normality (37, 43) as in the other studies.

The three youngest groups represented in figure 1 are from the studies of Kennedy and co-workers (87, 88). Their values for cerebral metabolic rate in the first decade of life are considerably higher than those obtained by Baird & Garfunkel (6) whose results indicated the same cerebral oxygen consumption in childhood as in adulthood. However, their subjects included patients with neurological disease, mental deficiency and similar conditions which could be responsible for a reduced cerebral metabolic rate and are, therefore, probably not representative of the normal state. If the data of Kennedy and associates are truly representative, then the cerebral oxygen consumption in the middle of the first decade of life can account for as much as 50 per cent of the total basal body oxygen consumption (87).

*Relationship between Metabolic Rate and Functional Activity in the Central Nervous System*

In organs such as the heart or skeletal muscles which perform mechanical work, increased functional activity is clearly associated with increased metabolic rate. In nervous tissues outside the central nervous

system, the electrical activity is an almost quantitative indicator of the degree of functional activity; and in such nervous structures as the sympathetic ganglia or postganglionic axons (17, 55, 110, 111, 113), increased electrical activity produced by electrical stimulation is definitely associated with an increased consumption of oxygen. On the other hand, in the central nervous system the over-all electrical activity of heterogeneous units cannot always be readily interpreted in terms of over-all functional activity. Therefore, in the central nervous system the relationship between functional activity and metabolic rate is less easily determined. Convulsive activity, hardly a normal condition, has often been resorted to as evidence of increased functional activity.

In the cerebral cortex of the cat, Davies and co-workers by means of the oxygen electrode found increases in oxygen utilization following electrical stimulation (21) or during convulsions (22) induced by pentylenetetrazol. Since the increased oxygen consumption either coincided with or followed the onset of convulsions, it was interpreted that the elevated metabolic rate was the result of the increased functional activity produced by the convulsive state. Geiger & Magnes (51) observed a similar relationship in the perfused cat brain during pentylenetetrazol and strychnine convulsions. Despite the increased oxygen consumption, glucose uptake in the perfused cat brain is markedly reduced during the convulsion but is enhanced immediately afterward (52). In the lightly anesthetized monkey, Schmidt and co-workers (162) found an excellent correlation between cerebral oxygen uptake and cerebral functional activity, the latter judged by muscular movements, ocular reflexes, character of respiration and level of arterial pressure. Changes in cerebral functional activity either occurred spontaneously, were caused by altering cerebral blood flow by means of hemorrhage, transfusion or epinephrine infusion, or were induced by convulsant (picrotoxin, pentylenetetrazol, nikethamide) or depressant (thiopental) drugs. Cerebral oxygen consumption rose to double the resting level during convulsions and was depressed to half the resting level in the post-convulsive state. Narcotic doses of thiopental lowered the metabolic rate about the same amount. In human beings no observations during convulsions have been made, but Kety and his associates (103) found similarly reduced cerebral metabolic rates in the mentally depressed state immediately following electroshock-induced convulsions. This reduction could not be attributed to insufficient cerebral blood flow which, although reduced, was still adequate.

Indeed, in human studies, convincing correlations between cerebral metabolic rate and mental activity have been obtained in a variety of pathological states of altered consciousness (39, 92). Graded reductions in cerebral oxygen consumption have been found to be associated with comparably graded reductions in mental alertness down to the level of coma in conditions such as diabetic acidosis and coma (99), uremic coma (73, 155), hepatic coma (39, 192), acute alcoholic intoxication (8), anesthesia (83, 193), cerebral ischemia due to shock (42) or increased intracranial pressure (102), neurosyphilis (74, 138), and organic dementia of various causes (115) (see table 3).

On the other hand, normal or physiological alterations in mental functions do not appear to be associated with any alterations in oxygen consumption of the brain as a whole. During natural sleep (121) and the performance of mental arithmetic (177), conditions which according to the electroencephalographic patterns are associated with decreased and increased cortical activity, respectively, the over-all cerebral metabolic rate is unchanged. In schizophrenia in which mental functions are qualitatively though not necessarily quantitatively altered, one study reported a fall in cerebral metabolic rate in cases of long duration (63), but others have found no differences from normal (103, 178). Some evidence is available that anxiety may in some circumstances be associated with an accelerated cerebral metabolic rate (92, 173) but this effect may be secondary to the calorigenic action on the brain of increased circulating amounts of epinephrine (104, 173). The lack of correlation between physiological alterations in mental activity and over-all cerebral metabolic rate is not necessarily evidence against a relationship between functional activity and metabolic rate in the central nervous system. In the pathological states, large segments of the brain are probably affected functionally in the same direction. In the physiological alterations in mental activity, the activity of only a small portion may be changed; or, as is more likely in a heterogeneous organ like the brain in which so many parts are functionally inversely related, there may be simply a redistribution of the patterns of activity among the various component parts so that the net metabolic rate of the brain as a whole may be only negligibly changed, if at all. Such heterogeneity during changes in mental function have been demonstrated as regards the blood flow in studies of the

TABLE 3. *Human Cerebral Metabolic Rate in Various Abnormal States Associated with Impaired Mental Function*

| Metabolic Defect | Condition | Mental State | Cerebral Oxygen Consumption (ml/100 g min) | References |
|---|---|---|---|---|
| None | Normal | Normal | 3.5* | |
| No alteration in metabolic rate (No significant difference from normal or control levels) | Schizophrenia | Distorted | 2.7, 3.3, 3.9 | 63, 103, 178 |
| | LSD-25 intoxication | Distorted | 3.9 | 178 |
| | Chlorpromazine sedation | Tranquilized | 2.5 | 35 |
| | Barbiturate semi-narcosis | Sedated | 3.3 | 103 |
| | Mild alcoholic inebriation | Mild intoxication | 2.7, 2.8 | 8, 35 |
| Insufficient nutrient supply: | | | | |
| Cerebral ischemia (oxygen and glucose lack) | Secondary shock | Generally stuporous or comatose | 1.9 | 42 |
| | Increased intracranial pressure | Comatose | 2.5 | 102 |
| Glucose lack | Insulin hypoglycemia | Confused | 2.6 | 103 |
| | Insulin coma | Comatose | 1.9 | 103 |
| Intracellular defects | Diabetic acidosis | Confused | 2.7 | 99 |
| | Diabetic coma | Comatose | 1.7 | 99 |
| | Irreversible postanoxic coma (after strangulation) | Comatose | 1.7 | 39 |
| | Irreversible posthypoglycemic coma | Comatose | 1.5 | 38 |
| | Irreversible postischemic coma (after cardiac arrest) | Comatose | 1.8 | 39 |
| | Uremic coma | Comatose | 2.2 | 73 |
| | Hepatic coma | Comatose | 1.6, 1.7 | 44, 192 |
| | Acute alcoholic intoxication | Stuporous or comatose | 2.2 | 8 |
| | Delirium tremens | Confused | 2.4 | 9 |
| | Barbiturate intoxication | Comatose | 2.3 | 39 |
| | Thiopental anesthesia | Comatose | 2.1, 2.1 | 83, 193 |
| | Steroid anesthesia | Comatose | 1.7 | 61 |
| | Dementia paralytica | Confused | 2.1, 2.2 | 74, 138 |

* Median of reported mean values (see table 1 for list of references).

local circulation of the cat brain (109, 174), and changes in blood flow may reflect simply the alterations in the functional and metabolic activity of the tissues subserved.

The metabolic rate indicates only the gross energy requirements of the brain. Determination of the changes in concentrations of various intermediate metabolites in brain tissue sampled from animals during various experimental states has yielded some information on the pathways of energy transfers and the nature of some of the intermediate biochemical processes associated with functional activity (141). For example, in the cat brain Olsen & Klein (136) found during convulsions a decreased concentration of glucose, glycogen, adenosine triphosphate and creatine phosphate, and an increase in adenosine diphosphate, inorganic phosphate and lactic acid. Pyruvate and hexosephosphate were relatively unchanged (136). The results of similar studies in rat brain were in general the same (27). These changes, indicative of an elevated rate of glycolysis and a depletion of high-energy phosphate stores, reflect the higher energy demand of the increased functional activity associated with convulsions. In addition, studies in rats have demonstrated cyclic decreases and restorations of the acetylcholine levels in the brain during electrically induced convulsions (142) and a significant liberation of ammonia in association with electrical or other types of stimulation (143). During anesthesia, a condition of reduced functional activity, changes in the opposite direction occur. Thus, the lactic acid content of the brain is reduced and the creatine phosphate and ATP contents increased (141), changes indicative of a decreased

energy utilization. There is also a decrease in the concentration of ammonia (143) and an increase in the acetylcholine level (142) in the brain. In the mouse brain during pentobarbital anesthesia, a reduction in the rates of synthesis of nucleoprotein and phospholipids also has been observed (28). Comparable changes in these various brain constituents have been observed to occur with changing physiological conditions. Thus, in rat brains lactic acid (144) was found to be reduced and acetylcholine (142) increased during natural sleep, while during excitement reverse changes occurred. Phosphate esters were little affected during either sleep or excitement (144). In general, the changes in brain constituent concentrations which are associated with altered cerebral activity follow the patterns to be expected from the altered energy demands of the functional states, increased and decreased activity giving evidence of increased and decreased rates of glycolysis and high-energy phosphate bond degradation, respectively.

### *Effects of Altered Body Temperature on Cerebral Metabolic Rate*

Studies in animals clearly demonstrate that cerebral oxygen consumption is reduced when significant lowering of body temperature, for example below 30°C, is achieved by lowering the environmental temperature (50, 106, 150). In one of these studies in dogs with body temperatures between 22°C and 27°C (106), cerebral blood flow was found to be so reduced, perhaps because of the increased viscosity of the blood, that despite the depressed metabolic rate, a relative cerebral ischemia and anoxia was present. The cerebral respiratory quotient (R.Q.) remained unchanged. In another study in hypothermic dogs both cerebral blood flow and oxygen consumption fell linearly and proportionately to levels at 26°C, equal to approximately one third of normal (150). There was, therefore, no evidence of cerebral anoxia. In cats cerebral oxygen consumption falls even more rapidly in hypothermia than does blood flow, clearly indicating a primary reduction in cerebral metabolic rate (50). The effects of lowered body temperature in man have not yet been reported.

The results of studies on the effects of increased body temperature are still somewhat confusing. A rise from 24°C to 34°C in the environmental temperature of one-day-old rats, which are poikilothermic, reduces their survival time under anoxic conditions to less than half (36), evidence of an increased demand for oxygen at the elevated temperatures. No such effect is observed in the adult rat which, however, is homoiothermic and probably maintains a normal body temperature under such conditions. In neurosyphilitic adult man, Himwich and co-workers (77) found an increase in arteriovenous oxygen difference during fever induced by the inductotherm, or the injection of typhoid vaccine or malarial parasites. Looney & Borkovic (119) found no such change in a similar group of patients treated with hyperpyrexia. The only quantitative study reported thus far in man is that of Heyman and associates (74) who found in both asymptomatic and symptomatic neurosyphilitic patients treated with fever therapy no significant increase in either cerebral arteriovenous oxygen difference or cerebral oxygen consumption with increased body temperature. However, since neurosyphilis can be associated with cerebral metabolic abnormalities as indicated by the depressed cerebral metabolic rate in the symptomatic patients (138), it would be of interest to repeat such studies in normal man.

## METABOLISM OF THE CENTRAL NERVOUS SYSTEM IN VARIOUS PATHOLOGICAL STATES

Much of our present knowledge of the metabolism of the central nervous system is derived from observations in functionally abnormal states, and many of these observations have been made in man. In table 3 are tabulated some of the results obtained in studies of the human cerebral metabolic rate in various pathological states, some occurring spontaneously, others artificially induced by pharmacological agents. All are characterized by clear evidence of mental and, therefore, cerebral dysfunction. It can be seen that those conditions which exhibit alterations in cerebral metabolic rate can be readily classified according to the general nature of the cerebral metabolic defect.

### *Inadequate Nutrient Supply*

CIRCULATORY DEFICIENCY. The effects of reduction of cerebral blood flow upon brain metabolism in experimental and clinical conditions have been described in a previous part of this chapter. It may be added that prolonged impairment of the cerebral circulation produced, for example by cardiac arrest, rapidly leads to irreversible intracellular metabolic changes

in the brain characterized by unconsciousness and a low cerebral metabolic rate, even long after the restoration of an adequate cerebral blood flow (39).

OXYGEN DEFICIENCY. Although cerebral blood flow is elevated by decreases in the oxygen tension of the arterial blood, this compensation may be insufficient to supply adequate amounts of oxygen to the brain (101). The progressive mental disturbances resulting from anoxia at high altitudes are well known (127). When the cerebral venous oxygen saturation drops to approximately 24 per cent (corresponding to approximately 15 mm Hg oxygen tension in the usual cerebral venous blood), consciousness is lost (117). Normally, the oxygen saturation and tension of cerebral venous blood are approximately 65 per cent and 35 mm Hg, respectively. Mild mental symptoms may, however, occur above the level of unconsciousness even though no discernible change in cerebral oxygen consumption occurs (101). It is possible that despite a normal rate of oxygen utilization, normal energy transfer does not occur at such low oxygen tensions in the brain. It is more likely, however, that mental symptoms short of unconsciousness can result from disturbances in areas of the brain so small that changes in their oxygen consumption are not reflected in measurements of the brain as a whole. Increased arterial oxygen tensions as high as those produced by the breathing of oxygen at 3.5 atm., a level close to the point of oxygen toxicity, is also unassociated with any change in cerebral metabolic rate (108).

Reduction in cerebral oxygen consumption has been reported in various chronic anemias (72) and in pernicious anemia (154), diseases in which arterial oxygen content rather than tension is decreased. Successful treatment of the pernicious anemia only partially restored the normal metabolic rate, evidence either of an irreversible effect of a prolonged oxygen deficiency in the brain or of some other intracellular effect of the disease quite independent of the anemia. Changes in mental function closely paralleled the changes in cerebral oxygen consumption. It must be pointed out, however, that the reduction in cerebral oxygen consumption observed in the anemias may be the result of a methodological error in the application of the nitrous oxide technique—the use of a brain-blood nitrous oxide partition coefficient uncorrected for the anemia (96).

Prolonged cerebral anoxia leads to irreversible intracellular metabolic changes. In a case of strangulation estimated to have lasted 10 min., studies done 5 days later while the patient was still in coma revealed a lowered oxygen utilization by the brain despite a normal cerebral blood flow and oxygen supply (39).

As for the effect of cerebral oxygen deficiency on the intermediary metabolism of the brain, studies in animals have demonstrated changes compatible with an increased rate of glycolysis and a depletion of energy-rich phosphate compounds. In dogs, the inhalation of 5 to 10 per cent oxygen results in relatively little change in glycogen or glucose contents, a marked increase in lactic acid and a lesser one in inorganic phosphate concentrations, and a fall in the phosphocreatine level of the brain (70). Little change in the ATP level was observed, probably because of its maintenance by the creatine phosphate still present. In cats (105) and in rats (2) similar effects were observed following the administration of cyanide except that the ATP level was also markedly decreased.

GLUCOSE DEFICIENCY. A deficiency of the other essential nutrient, glucose, is also associated with disturbances of mental function, which have been described in a previous part of this chapter. The metabolic aspects of coma resulting from administration of insulin, however, deserve further consideration. In the studies of Kety and co-workers (103), at arterial glucose levels of 8 mg per cent, cerebral oxygen consumption fell to 1.9 ml per 100 gm per min. and cerebral glucose utilization was negligible. Accordingly, other substances must have been oxidized. Since the R.Q. remained approximately unity, however, these substances must have been predominantly carbohydrate, derived probably from the carbohydrate stores within the brain which have been found to be depleted in insulin hypoglycemia (90, 135). Since the total stores of glycogen and glucose within the human brain have been estimated to be equivalent to approximately 2 gm of glucose (90, 92), at the low rate of cerebral oxygen consumption in insulin coma these stores would be depleted in about 90 min. Indeed, this is about the time limit beyond which insulin coma results in irreversible changes in the brain (92), a development which might, perhaps, be attributed to irreversible intracellular damage resulting from the oxidation of structural and enzymatic components of the brain following the exhaustion of carbohydrate stores. In such cases, coma and a remarkably low rate of cerebral oxygen consumption persist until death (38). Glucose can no longer reverse this picture even when it is administered in amounts sufficient to produce

hyperglycemia (38, 39). Unfortunately, the cerebral R.Q., which might indicate the nature of the substrate being consumed by the brain, has not been reported in such cases. The finding by Geiger & Yamasaki (54) of the requirement of liver factors, subsequently shown to be replaceable by the pyrimidine nucleosides, cytidine and uridine, for the continued normal utilization of glucose by the perfused cat brain may be of relevance here. In their absence, the levels of galactosides and phospholipids in the brain decrease and the ability to utilize glucose progressively fails, both changes reversible by the replacement of the nucleosides. The failure to utilize administered glucose is one of the defects which develops in irreversible posthypoglycemic coma.

The change which occurs in the intermediary metabolites within the brain during insulin hypoglycemia or coma reflects only the expected effects of glucose lack and the reduction in energy availability. Thus, glycogen, glucose and lactic acid levels in the cat brain have been found to be decreased, and there is a degradation of high-energy phosphate compounds, such as creatine phosphate and ATP, to inorganic phosphate (135).

*Intracellular Defects*

A number of disturbances of cerebral function and metabolism must by exclusion be attributed to intracellular defects (table 3). Those which result from an excessively prolonged deficiency of either or both of the essential nutrients, oxygen and glucose, have already been discussed. There are others, however, which cannot be related to the nutrient supply to the brain.

SYSTEMIC METABOLIC DISEASE. Several metabolic diseases with broad systemic manifestations, including impairment of cerebral functions, have been studied in man. Diabetes mellitus, when permitted to progress to the stage of acidosis and ketosis, leads to mental confusion and ultimately to deep coma with parallel proportionate reductions in cerebral oxygen consumption (99) (table 3). In diabetic acidosis in which both mental function and cerebral metabolic rate were only moderately depressed, Kety and his associates (99) found the mean cerebral R.Q. to be 0.92 or within normal limits. In deep coma the cerebral R.Q. was 0.88, a value significantly reduced from the normal level. This change in R.Q. may be meaningful, but the low blood carbon dioxide levels found in this condition make accurate analysis of this metabolic function difficult. Both the functional and metabolic disturbances of the brain in diabetic acidosis unassociated with coma were completely reversible by adequate insulin therapy; of the six patients in deep coma, only one survived despite rigorous therapeutic measures (99). Kety (95) has found in diabetic acidosis evidence for a slight but significant production, 0.91 mg per 100 gm per min., of lactic acid by the brain. There was no evidence of cerebral utilization or production of $\alpha$-ketoglutarate and pyruvate, nor of total ketones which are elevated in the blood in this disease. Neither the nature of the metabolic defect nor the cause of the depressed cerebral metabolic rate are known. Deficiency of nutrient material cannot be implicated as a cause of the cerebral disturbances since blood glucose is elevated, and cerebral blood flow and oxygen supply are more than adequate (99). Neither is the insulin lack, which is presumably the basis of the systemic manifestations of the disease, a likely cause of the cerebral abnormalities since no direct role of this hormone in the cerebral metabolism has been demonstrated and, indeed, there is evidence to the contrary (180). Ketosis may be severe in this disease, and there is conflicting evidence that a rise in the blood level of one of the ketones, acetoacetate, can cause coma in animals (30, 47, 86, 163). Kety and his associates (99) in their studies of diabetic acidosis and coma did observe a significant correlation between the depression of cerebral metabolic rate and the degree of ketosis. However, they also obtained an almost equally good correlation with the degree of acidosis. It is possible that either the ketosis or the acidosis may be responsible for the defect in the cerebral functions, but it is more likely that they are both reflections of some other more directly responsible metabolic disturbance (47).

Coma is occasionally associated with severe impairment of liver function, as, for example, in cirrhosis of the liver. In patients in hepatic coma, Fazekas and co-workers (44), and Wechsler and his associates (192) have found the cerebral oxygen consumption to be profoundly depressed. Cerebral blood flow is also moderately depressed; but since there is no evidence of any significant impairment of the nutrient supply, the low cerebral oxygen consumption reflects only a reduced metabolic demand in the brain. Bessman & Bessman (14) have found in such cases a significant positive arterial-cerebral venous ammonia difference, evidence for the cerebral uptake of ammonia by the brain, and the degree of coma and the arteriovenous difference were both roughly proportional to the

degree of elevation of the ammonia level in the arterial blood. In all the cases of hepatic failure, whether coma was present or not, the blood ammonia concentration was elevated. A similar correlation between the blood ammonia level and the occurrence of coma following meat ingestion has been reported in a patient with cirrhosis and an Eck fistula (126). On the basis of these observations, Bessman & Bessman (14) have postulated that hepatic coma and the reduced metabolic rate associated with it result from a slowing of the tricarboxylic cycle in the brain because of the diversion of α-ketoglutarate by reductive amination, a process accelerated by the higher uptake of ammonia by the brain in this disease. The product of this reaction is glutamate, and these authors have found an increase in the glutamate produced by the brain in hepatic coma (13). This hypothesis, although interesting and ingenious, is somewhat tenuous in view of the findings of other investigators of a lack of correlation between the degree of coma and the arterial blood ammonia level (44, 189). Indeed, coma has been observed in the absence of an increase in the ammonia concentration of the blood (39, 44).

Depression of both mental function and cerebral metabolic rate has been observed in uremic coma (73, 155). The chemical basis of the functional and metabolic disturbances in the brain in this condition also remains undetermined.

In the comatose states associated with these systemic diseases, there is a depression of both metabolic rate and cerebral function. From the available evidence, it is impossible to state which, if either, is the primary change. It is possible that the depressions of both functions, although well correlated with each other, are actually independent reflections of a more general impairment of neuronal processes by some unknown factors incident to the disease.

ANESTHESIA. The state of unconsciousness produced by anesthetic agents is similarly associated with marked depression of the cerebral metabolic rate. Reductions in the cerebral oxygen consumption comparable to those occurring in the comas of the metabolic diseases have been observed during thiopental anesthesia in man (83, 193), in the monkey (162) and in the perfused cat brain (51). Recently the steroid, 21-hydroxypregnane-3,20-dione sodium succinate, has been found to produce anesthesia in man with the same depression in cerebral oxygen consumption (61, 64). The reduced metabolic rate is the result of a depressed cerebral oxygen demand and not of a reduction in cerebral blood flow or nutrient supply. Quastel (139) has suggested that anesthetics act primarily by interference with the intracellular oxidation of glucose. Bain (5) has found *in vitro* that barbiturates depress oxidative phosphorylation. Either of these mechanisms would decrease the availability of energy to the brain. The results of studies of the intermediate metabolites in the anesthetized brain are not compatible with these mechanisms. During anesthesia there is a reduction in the lactic acid and an increase in the ATP and phosphocreatine levels in the brain (141, 182, 183); the brain acetylcholine level is increased and that of ammonia reduced (141–143). These changes, the opposite of those observed with increased energy demand as, for example, in convulsions, are indicative of a reduction in energy utilization rather than of energy availability. They are more compatible with the view suggested by the findings of Larrabee and associates (110, 112, 113) that anesthetics act by blocking synaptic transmission, thus reducing neuronal interaction and functional activity and, consequently, metabolic demands. The same mechanism has been postulated for the depressed cerebral metabolic rate following lobotomy in man (170).

CONVULSIVE DISORDERS. The metabolic consequences of the induction of convulsions have been discussed above in the section on functional activity and metabolism. The cerebral metabolic rate during convulsive seizures has not yet been measured in man. A series of electroconvulsive treatments, however, does not appear to cause any permanent alteration of cerebral metabolic rate (196). In studies during the interseizure period, Grant and associates (65) found a normal rate of cerebral oxygen consumption in adult epileptic patients, but Kennedy (unpublished observations) has found moderate reductions in children with the same disease. Preliminary observations indicate that in those children who show signs of deterioration or mental retardation, the reduction in cerebral metabolic rate is even greater (Kennedy, unpublished observations).

Some biochemical studies which suggest interrelations between abnormalities of brain tissue metabolism and convulsive activity are of special interest. In human cerebral cortical tissue excised from epileptogenic foci, elevated cholinesterase activity, impaired production of 'bound' acetylcholine and abnormal metabolism of glutamic acid have been described (184, 186, 187). These metabolic defects were reversed *in vitro* by the addition of glutamine,

asparagine or ATP (185, 186, 188), and clinical trials of L-glutamine and L-asparagine in epilepsy have been reported to result in some degree of control of clinical seizures (185, 186). Pyridoxine deficiency and pyridoxine antagonists have been found to cause epileptiform seizures in man (171, 172, 186) and animals (186). This finding may be of major significance in view of the recently uncovered role of this vitamin in the form of pyridoxal-5′-phosphate as a coenzyme in the transamination and decarboxylation reactions of some of the amino acids of obvious importance in the metabolism of the central nervous system (186). Indeed, the suggestive findings that γ-aminobutyric acid, the product of the decarboxylation of glutamate, a pyridoxal-5′-phosphate dependent reaction peculiar to the nervous system (4, 146–149, 191, 197), may be a chemical mediator of functional inhibition in the central nervous system (10, 32, 71) leads to intriguing possibilities not only concerning the chemical abnormalities in epileptiform seizures but also regarding the fundamental chemical mechanisms underlying the normal functions of the central nervous system.

MISCELLANEOUS DISORDERS. A number of other states of disordered function of the central nervous system have been studied, some with and others without gross evidence of deranged metabolism. In table 3 are included a few of those which have been observed in human patients and found to be associated with alterations in the cerebral metabolic rate. Since no serious impairment in cerebral blood flow or nutrient supply has been found in these conditions, the functional and metabolic disturbances have been considered to be the results of unknown intracellular defects. Thus, there have been found to be concomitant reductions in mental function and cerebral metabolic rate in acute alcoholic intoxication (8), in delirium tremens (9), in barbiturate intoxication (39), in neurosyphilis when dementia paralytica is present (74, 138), and in organic dementia of various types (115). Freyhan and his associates (48) found a low cerebral oxygen consumption in senile psychosis, both with and without cerebral arteriosclerosis, but others have reported similarly low values in elderly nonpsychotic subjects (37, 169). In schizophrenia, a disease of obvious qualitative though not necessarily quantitative changes in mental function, there is no clear evidence of any alteration in cerebral metabolism. Gordan and co-workers (63) have reported reduced values for cerebral oxygen consumption in cases of greater than 4 years duration, but these findings are in disagreement with the results of other studies (103, 178). In multiple sclerosis in which the functional defect is more neurological than psychological, no alteration in cerebral metabolic rate has been observed (1, 156). However, during exacerbations of the disease, the brain was found by Adams and co-workers (1) to take up glutamine and release glutamate in equivalent amounts, a pattern opposite to that observed in the normal state. The administration of succinate occasionally reversed the pattern toward normal without any significant change in metabolic rate. Since it is the amidation of glutamate by ammonia to form glutamine which is apparently involved in this abnormal pattern, these workers (1) suggest that inadequate detoxification of ammonia in the central nervous system may play a role in the pathogenesis of multiple sclerosis.

## EFFECTS OF HORMONES AND DRUGS ON IN VIVO METABOLISM OF THE CENTRAL NERVOUS SYSTEM

### *Hormones and Related Drugs*

THYROID HORMONE. The accelerative effect which the thyroid hormone has been found to have on the metabolic processes of almost all body tissues does not seem to occur in the brain. In human adults suffering from hyperthyroidism, no alteration in cerebral oxygen consumption has been observed despite marked increases in the total body metabolic rate (153, 165, 179). The picture in hypothyroidism is less clear. In adult hypothyroid patients one study found a reduction in cerebral metabolic rate (159); another found no difference from normal during the disease and no change following effective thyroid medication (165). In juvenile hypothyroidism, for example cretinism, Himwich and co-workers (79) found by means of cerebral arteriovenous oxygen differences and the thermoelectric flow recorder qualitative evidence of an increase in cerebral metabolic rate following thyroid administration. In studies in rats Fazekas and his co-workers (40) found in artificially induced hyperthyroidism that the cortical oxygen consumption rose more rapidly from its postnatal low level to the normal adult level. Once the level of the mature state was attained, there was no difference in the cortical oxygen consumptions of the hyperthyroid and normal rats. No differences from normal were observed in hypothyroidism. From all this evidence, it appears that the thyroid hormone exerts its effect on the brain chiefly during its period of growth and development. Once maturation has

been achieved the brain appears to be little affected, if at all, by the level of circulating thyroid hormone. Preliminary observations indicate that this lack of effect is not the result of the inability of thyroxine to pass the blood-brain barrier (unpublished observations). It may, perhaps, reflect more a role for thyroxine in the metabolism of the brain when the synthesis of proteins and other structural and enzymatic components utilize a prominent portion of the total energy consumption, as during growth and maturation, but little influence of the hormone when development is complete and the energy now derived almost exclusively from the metabolism of carbohydrates is utilized chiefly for the support of cerebral functional activity (179).

PITUITARY, ADRENAL CORTICAL AND SEX HORMONES. The relatively few reported studies, particularly in man, on the effects of the pituitary, adrenal cortical and sex hormones on the metabolism of the central nervous system *in vivo*, with a few exceptions, indicate very little effect of these hormones, at least in the mature individual. In human adult patients with preadolescent hypopituitarism, who on an endocrine basis had not developed through puberty, Gordan (61) found significantly elevated values for cerebral oxygen consumption similar to those observed by him in preadolescent testicular eunuchoidism (61). Since the former group is characterized by low and the latter group by high circulating pituitary gonadotropin, it cannot be this hormone which is involved in the altered cerebral metabolic rate. In castrated prepubertal rats there is similarly an elevated cerebral oxygen consumption (29, 33, 61), and this is restored to normal by the administration *in vivo* of any one of a number of steroids, testosterone, methyltestosterone, epitestosterone, progesterone, anhydrohydroxyprogesterone, desoxycorticosterone acetate and corticotropin, but not by estradiol-17$\beta$ (34, 61). An additional steroid, 21-hydroxypregnane-3,20-dione, has recently been found to produce in endocrinologically normal man, not only a profound reduction in cerebral oxygen consumption but anesthesia as well (61, 64). Gordan (61) suggests, therefore, that the androgenic and adrenal cortical steroids normally maintain a 'braking' action on the cerebral metabolic rate, and when deficient, as in preadolescent testicular eunuchoidism or preadolescent hypopituitarism, there is a release and elevation of the cerebral metabolic rate. He further postulates that the steep fall in human cerebral metabolic rate at puberty (87) is the result of the increased production of these steroid hormones at that time (61, 62). On the other hand, in postpubertal human males, castration has been reported to cause a fall in cerebral oxygen consumption, and the postoperative administration of the steroids, desoxycorticosterone glucoside or testosterone, cause, if anything, a rise in the cerebral metabolic rate back toward the precastration level (61). As for other adrenocortical hormones, Bergen and co-workers (11) have observed in adrenalectomized animals a fall in cerebral metabolic rate which was restored to normal by adrenocortical extract and cortisone but not by desoxycorticosterone. In man neither adrenocorticotrophic hormone (3, 160, 167) nor cortisone (167) have been found to have any significant effect on cerebral metabolic rate.

ADRENAL MEDULLARY HORMONES. The first chemical agent to be found to accelerate the cerebral metabolic rate in normal man is the adrenal medullary sympathomimetic amine, *l*-epinephrine. When administered by continuous intravenous infusion in sufficient amounts to raise the arterial pressure, it was found to produce consistent and significant increases in the rate of cerebral oxygen consumption (104). Because of the relationship of this substance to the phenomenon of 'anxiety,' it has been suggested that it is the mediator of the stimulation of cerebral metabolic rate in that emotional state (173). Sensenbach and his associates (166) have failed to find any effect of *l*-epinephrine on human cerebral metabolic rate, but they administered the drug intramuscularly in doses insufficient to alter the arterial blood pressure. Recently, mephentermine, a synthetic amine closely related to epinephrine, has been found also to raise the cerebral metabolic rate when administered intravenously in pressor doses (140). The other adrenal medullary amine, *l*-norepinephrine, does not appear to have any obvious effect on cerebral metabolism (104, 166).

### *Psychosomimetic and Tranquilizing Drugs*

Considerable interest has recently been focused on two classes of drugs which appear to be capable of producing profound alterations in psychological functions. One class, the psychosomimetic drugs, is reputed to produce mental symptoms which simulate those of the spontaneously occurring psychoses such as schizophrenia (145, 181). The other class, the tranquilizing or ataractic drugs, has been employed clinically for the alleviation or amelioration of many

of the symptoms associated with various neurotic and psychotic disturbances. The classical psychosomimetic drug, lysergic acid diethylamide (LSD-25), has been found to be without effect on the cerebral oxygen and glucose metabolism in both normal man and schizophrenic patients, even when administered in doses sufficient to produce its characteristic psychological effects (178). Chlorpromazine, one of the more commonly employed tranquilizing drugs, has also been found to be without effect on the human cerebral oxygen consumption (35, 130). It does, however, cause an elevation of the ATP level, probably by reduced utilization, in various parts of the rat brain, chiefly in the midbrain but also to a lesser extent in the cerebellum, cerebral cortex and medulla, in that order (68). The paucity of alterations in cerebral metabolism found in states of altered psychological functions, such as exist in schizophrenia or are produced by agents such as the psychosomimetic and tranquilizing drugs, suggests that these functions involve processes too subtle to be detected by our present technique, or metabolic systems not yet subjected to our investigations. Psychological functions appear to be a product not only of the metabolic processes within the cells but probably to a far greater extent of the interaction of the neurons of the central nervous system. They represent the ultimate development of the main function of the nervous system, which is communication, and their understanding awaits the unraveling of the physicochemical mechanisms underlying the processes of communication among the cellular elements of that system.

## REFERENCES


1. Adams, J. E., H. A. Harper, G. S. Gordan, M. Hutchin and R. C. Bentinck. *Neurology* 5: 100, 1955.
2. Albaum, H. B., J. Tepperman and O. Bodansky. *J. Biol. Chem.* 164: 45, 1946.
3. Alman, R. W. and J. F. Fazekas. *A. M. A. Arch. Neurol. & Psychiat.* 65: 680, 1951.
4. Awapara, J., A. J. Landua, R. Fuerst and B. Scale. *J. Biol. Chem.* 187: 35, 1950.
5. Bain, J. A. *Fed. Proc.* 11: 653, 1952.
6. Baird, H. W. and J. M. Garfunkel. *J. Pediat.* 42: 570, 1953.
7. Batson, O. V. *Fed. Proc.* 3: 139, 1944.
8. Battey, L. L., A. Heyman and J. L. Patterson. *J. A. M. A.* 152: 6, 1953.
9. Battey, L. L., J. L. Patterson and A. Heyman. *Am. J. Med.* 13: 105, 1952.
10. Bazemore, A., K. A. C. Elliot and E. Florey. *Nature, London* 178: 1052, 1956.
11. Bergen, J. R., C. A. Hunt and H. Hoagland. *Am. J. Physiol.* 175: 327, 1953.
12. Bernsmeier, A. and K. Siemons. *Arch. ges. Physiol.* 258: 149, 1953.
13. Bessman, S. P. and A. N. Bessman. *Fed. Proc.* 13: 336, 1954.
14. Bessman, S. P. and A. N. Bessman. *J. Clin. Invest.* 34: 622, 1955.
15. Björk, V. O. *Acta chir. scandinav.* Suppl. 96: 137, 1948.
16. Brazier, M. A. B., J. E. Finesinger and R. S. Schwab. *J. Clin. Invest.* 23: 313, 1944.
17. Bronk, D. W., M. G. Larrabee and P. W. Davies. *Fed. Proc.* 5: 11, 1946.
18. Chute, A. L. and D. H. Smyth. *Quart. J. Exper. Physiol.* 29: 379, 1939.
19. Coxon, R. V. *Biochem. Soc. Sympos.* 8: 3, 1952.
20. Dameshek, W., A. Myerson and C. Stephenson. *A. M. A. Arch. Neurol. & Psychiat.* 33: 1, 1935.
21. Davies, P. W., R. G. Grenell and D. W. Bronk. *Fed. Proc.* 7: 25, 1948.
22. Davies, P. W. and A. Rémond. *A. Res. Nerv. & Ment. Dis., Proc.* 26: 205, 1947.
23. Davis, E. W., W. S. McCulloch and E. Roseman. *Am. J. Psychiat.* 100: 825, 1944.
24. Davis, P. A. *Am. J. Physiol.* 133: 259, 1941.
25. Dawson, R. M. C. *Biochem. J.* 49: 138, 1951.
26. Dawson, R. M. C. *Biochem. Soc. Sympos.* 8: 93, 1952.
27. Dawson, R. M. C. and D. Richter. *Am. J. Physiol.* 160: 11, 1950.
28. Dawson, R. M. C. and D. Richter. *Proc. Roy. Soc., London. ser. B* 137: 252, 1950.
29. Denison, M. E., R. L. Jasper, W. A. Hiestand and M. X. Zarrow. *Fed. Proc.* 14: 37, 1955.
30. Dodds, E. C. and J. D. Robertson. *Lancet* 218: 852, 1930.
31. Dumke, P. R. and C. F. Schmidt. *Am. J. Physiol.* 138: 421, 1943.
32. Edwards, C. and S. W. Kuffler. *Fed. Proc.* 16: 34, 1957.
33. Eisenberg, E., G. S. Gordan and H. W. Elliott. *Science* 109: 337, 1949.
34. Eisenberg, E., G. S. Gordan and H. W. Elliott. *Fed. Proc.* 9: 269, 1950.
35. Fazekas, J. F., S. N. Albert and R. W. Alman. *Am. J. M. Sc.* 230: 128, 1955.
36. Fazekas, J. F., F. A. D. Alexander and H. E. Himwich. *Am. J. Physiol.* 134: 281, 1941.
37. Fazekas, J. F., R. W. Alman and A. N. Bessman. *Am. J. M. Sc.* 223: 245, 1952.
38. Fazekas, J. F., R. W. Alman and A. E. Parrish. *Am. J. M. Sc.* 222: 640, 1951.
39. Fazekas, J. F. and A. N. Bessman. *Am. J. Med.* 15: 804, 1953.
40. Fazekas, J. F., F. B. Graves and R. W. Alman. *Endocrinology* 48: 169, 1951.
41. Fazekas, J. F., J. Kleh and F. A. Finnerty. *Am. J. Med.* 18: 477, 1955.
42. Fazekas, J. F., J. Kleh and A. E. Parrish. *Am. J. M. Sc.* 229: 41, 1955.

43. Fazekas, J. F., J. Kleh and L. Witkin. *J. Am. Geriatrics Soc.* 1: 836, 1953.
44. Fazekas, J. F., H. E. Ticktin, W. R. Ehrmantraut and R. W. Alman. *Am. J. Med.* 21: 843, 1956.
45. Ferris, E. B., M. Rosenbaum, C. O. Aring, H. W. Ryder, E. Roseman and J. R. Hawkins. *A. M. A. Arch. Neurol. & Psychiat.* 46: 509, 1941.
46. Finnerty, F. A., L. Witkin and J. F. Fazekas. *J. Clin. Invest.* 33: 1227, 1954.
47. Fisher, P. *Am. J. M. Sc.* 221: 384, 1951.
48. Freyhan, F. A., R. B. Woodford and S. S. Kety. *J. Nerv. & Ment. Dis.* 113: 449, 1951.
49. Friedberg, F., H. Tarver and D. M. Greenberg. *J. Biol. Chem.* 173: 355, 1948.
50. Gänshirt, H., H. Hirsch, W. Krenkel, M. Schneider and W. Zylka. *Arch. exper. Path. u. Pharmakol.* 222: 431, 1954.
51. Geiger, A. and J. Magnes. *Am. J. Physiol.* 149: 517, 1947.
52. Geiger, A., J. Magnes and J. Dobkin. *Fed. Proc.* 13: 52, 1954.
53. Geiger, A., J. Magnes, R. M. Taylor and H. Waelsch. *Fed. Proc.* 8: 54, 1949.
54. Geiger, A. and S. Yamasaki. *Fed. Proc.* 15: 71, 1956.
55. Geraro, R. W. *Physiol. Rev.* 12: 469, 1932.
56. Gibbs, E. L., W. G. Lennox, L. F. Nims and F. A. Gibbs. *J. Biol. Chem.* 144: 325, 1942.
57. Gibbs, F. A. *Proc. Soc. Exper. Biol. & Med.* 31: 141, 1933.
58. Gibbs, F. A., H. Maxwell and E. L. Gibbs. *A. M. A. Arch. Neurol. & Psychiat.* 57: 137, 1947.
59. Goldfarb, W. and J. Wortis. *Quart. J. Stud. Alcohol* 1: 268, 1940.
60. Goldfarb, W. and J. Wortis. *Proc. Soc. Exper. Biol. & Med.* 46: 121, 1941.
61. Gordan, G. S. *Recent Progr. Hormone Res.* 12: 153, 1956.
62. Gordan, G. S. and J. F. Adams. In: *Hormones and the Aging Process*, edited by E. T. Engle and G. Pincus. New York: Acad. Press, 1956, p. 299.
63. Gordan, G. S., F. M. Estess, J. E. Adams, K. M. Bowman and A. Simon. *A. M. A. Arch. Neurol. & Psychiat.* 73: 544, 1955.
64. Gordan, G. S., N. Guadagni, J. Picchi and J. E. Adams. *Presse méd.* 63: 1483, 1955.
65. Grant, F. C., E. B. Spitz, H. A. Shenkin, C. F. Schmidt and S. S. Kety. *Tr. Am. Neurol. A.* 72: 82, 1947.
66. Gregg, D. E. and R. E. Shipley. *Fed. Proc.* 3: 144, 1944.
67. Grenell, R. G. and P. W. Davies. *Fed. Proc.* 9: 52, 1950.
68. Grenell, R. G., J. Mendelson and W. D. McElroy. *A. M. A. Arch. Neurol. & Psychiat.* 73: 347, 1955.
69. Grenell, R. G. and M. Wolbarsht. *XX Internat. Physiol. Congr., Proc.* 369, 1956.
70. Gurdjian, E. S., W. E. Stone and J. E. Webster. *A. M. A. Arch. Neurol. & Psychiat.* 51: 472, 1944.
71. Hayashi, T. and K. Nagai. *XX Internat. Physiol. Congr., Proc.* 410, 1956.
72. Heyman, A., J. L. Patterson and T. W. Duke. *J. Clin. Invest.* 31: 824, 1952.
73. Heyman, A., J. L. Patterson and R. W. Jones. *Circulation* 3: 558, 1951.
74. Heyman, A., J. L. Patterson and F. T. Nichols. *J. Clin. Invest.* 29: 1335, 1950.
75. Himwich, H. E., K. M. Bowman, C. Daly, J. F. Fazekas, J. Wortis and W. Goldfarb. *Proc. Soc. Exper. Biol. & Med.* 45: 468, 1940.
76. Himwich, H. E., K. M. Bowman, C. Daly, J. F. Fazekas, J. Wortis and W. Goldfarb. *Am. J. Physiol.* 132: 640, 1941.
77. Himwich, H. E., K. M. Bowman, J. F. Fazekas and W. Goldfarb. *Am. J. M. Sc.* 200: 347, 1940.
78. Himwich, H. E., K. M. Bowman, J. Wortis and J. F. Fazekas. *J. Nerv. & Ment. Dis.* 89: 273, 1939.
79. Himwich, H. E., C. Daly, J. F. Fazekas and H. C. Herrlich. *Am. J. Psychiat.* 98: 489, 1942.
80. Himwich, H. E. and J. F. Fazekas. *Endocrinology* 21: 800, 1937.
81. Himwich, H. E., Z. Hadidian, J. F. Fazekas and H. Hoagland. *Am. J. Physiol.* 125: 578, 1939.
82. Himwich, W. A. and H. E. Himwich. *J. Neurophysiol.* 9: 133, 1946.
83. Himwich, W. A., E. Homburger, R. Maresca and H. E. Himwich. *Am. J. Psychiat.* 103: 689, 1947.
84. Himwich, H. E. and L. H. Nahum. *Am. J. Physiol.* 88: 680, 1929.
85. Hoagland, H., M. A. Rubin and D. E. Cameron. *Am. J. Physiol.* 120: 559, 1937.
86. Hurtley, W. H. *Quart. J. Med.* 9: 301, 1915.
87. Kennedy, C. and L. Sokoloff. *J. Clin. Invest.* 36: 1130, 1957.
88. Kennedy, C., L. Sokoloff and W. Anderson. *A. M. A. Am. J. Dis. Child.* 88: 813, 1954.
89. Kerr, S. E. *J. Biol. Chem.* 116: 1, 1936.
90. Kerr, S. E. and M. Ghantus. *J. Biol. Chem.* 116: 9, 1936.
91. Kety, S. S. *Meth. med. Res.* 1: 204, 1949.
92. Kety, S. S. *Am. J. Med.* 8: 205, 1950.
93. Kety, S. S. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 208.
94. Kety, S. S. *J. Chron. Dis.* 3: 478, 1956.
95. Kety, S. S. In: *The Metabolism of the Nervous System*, edited by D. Richter. London: Pergamon Press, 1957.
96. Kety, S. S., M. H. Harmel, H. T. Broomell and C. B. Rhode. *J. Biol. Chem.* 173: 487, 1948.
97. Kety, S. S., W. M. Landau, W. H. Freygang, L. P. Rowland and L. Sokoloff. *Fed. Proc.* 14: 85, 1955.
98. Kety, S. S., F. D. W. Lukens, R. B. Woodford, M. H. Harmel, F. A. Freyhan and C. F. Schmidt. *Fed. Proc.* 7: 64, 1948.
99. Kety, S. S., B. D. Polis, C. S. Nadler and C. F. Schmidt. *J. Clin. Invest.* 27: 500, 1948.
100. Kety, S. S. and C. F. Schmidt. *J. Clin. Invest.* 27: 476, 1948.
101. Kety, S. S. and C. F. Schmidt. *J. Clin. Invest.* 27: 484, 1948.
102. Kety, S. S., H. A. Shenkin and C. F. Schmidt. *J. Clin. Invest.* 27: 493, 1948.
103. Kety, S. S., R. B. Woodford, M. H. Harmel, F. A. Freyhan, K. E. Appel and C. F. Schmidt. *Am. J. Psychiat.* 104: 765, 1948.
104. King, B. D., L. Sokoloff and R. L. Wechsler. *J. Clin. Invest.* 31: 273, 1952.
105. Klein, J. R. and N. S. Olsen. *J. Biol. Chem.* 167: 747, 1947.
106. Kleinerman, J. and A. L. Hopkins. *Fed. Proc.* 14: 410, 1955.

107. Lajtha, A., S. Furst, A. Gerstein and H. Waelsch. *J. Neurochem.* 1: 289, 1957.
108. Lambertsen, C. J., R. H. Kough, D. Y. Cooper, G. L. Emmel, H. H. Loeschke and C. F. Schmidt. *J. Appl. Physiol.* 5: 471, 1953.
109. Landau, W. H., W. H. Freygang, L. P. Rowland, L. Sokoloff and S. S. Kety. *Tr. Am. Neurol. A.* 80: 125, 1955.
110. Larrabee, M. G. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 384.
111. Larrabee, M. G. and D. W. Bronk. *Cold Spring Harbor Symp. Quant. Biol.* 17: 245, 1952.
112. Larrabee, M. G. and J. M. Posternak. *J. Neurophysiol.* 15: 91, 1952.
113. Larrabee, M. G., J. G. Ramos and E. Bülbring. *J. Cell. & Comp. Physiol.* 40: 461, 1952.
114. Lassen, N. A. and O. Munck. *Acta physiol. scandinav.* 33: 30, 1955.
115. Lassen, N. A., O. Munck and E. R. Tottey. *A. M. A. Arch. Neurol. & Psychiat.* 77: 126, 1957.
116. Lennox, W. G. *A. M. A. Arch. Neurol. & Psychiat.* 26: 719, 1931.
117. Lennox, W. G., F. A. Gibbs and E. L. Gibbs. *A. M. A. Arch. Neurol. & Psychiat.* 34: 1001, 1935.
118. Loman, J. *A. M. A. Arch. Neurol. & Psychiat.* 45: 282, 1941.
119. Looney, J. M. and E. J. Borkovic. *Am. J. Physiol.* 136: 177, 1942.
120. Maddock, S., J. E. Hawkins and E. Holmes. *Am. J. Physiol.* 125: 551, 1939.
121. Mangold, R., L. Sokoloff, E. Conner, J. Kleinerman, P. G. Therman and S. S. Kety. *J. Clin. Invest.* 34: 1092, 1955.
122. Mann, F. C. *Medicine* 6: 419, 1927.
123. Mann, F. C. and T. B. Magath. *A. M. A. Arch. Int. Med.* 30: 171, 1922.
124. Martin, H., R. Rodnight, H. McIlwain and M. A. Tresize. *Nature, London* 179: 419, 1957.
125. Mayer-Gross, W. and J. W. Walker. *Biochem. J.* 44: 92, 1949.
126. McDermott, W. V. and R. D. Adams. *J. Clin. Invest.* 33: 1, 1954.
127. McFarland, R. A. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 335.
128. McGinty, D. A. *Am. J. Physiol.* 88: 312, 1929.
129. McIlwain, H. *Biochem. Soc. Sympos.* 8: 27, 1952.
130. Morris, G., R. Pontius, R. Herschberger and J. H. Moyer. *Fed. Proc.* 14: 371, 1955.
131. Mulder, J. and L. A. Crandall. *Am. J. Physiol.* 137: 436, 1942.
132. Munck, O. and N. A. Lassen. *Circulation Res.* 5: 163, 1957.
133. Myerson, A., R. C. Halloran and H. L. Hirsch. *A. M. A. Arch. Neurol. & Psychiat.* 17: 807, 1927.
134. Nylin, G. and H. Blömer. *Circulation Res.* 3: 79, 1955.
135. Olsen, N. S. and J. R. Klein. *J. Biol. Chem.* 167: 739, 1947.
136. Olsen, N. S. and J. R. Klein. *A. Res. Nerv. & Ment. Dis., Proc.* 26: 118, 1947.
137. Page, W. R., W. J. German and L. F. Nims. *Yale J. Biol. & Med.* 23: 462, 1951.
138. Patterson, J. L., A. Heyman and F. T. Nichols. *J. Clin. Invest.* 29: 1327, 1950.
139. Quastel, J. H. *Physiol. Rev.* 19: 135, 1939.
140. Richardson, D. W., R. W. Ferguson and J. L. Patterson. *J. Pharmacol. & Exper. Therap.* 119: 219, 1957.
141. Richter, D. *Biochem. Soc. Sympos.* 8: 62, 1952.
142. Richter, D. and J. Crossland. *Am. J. Physiol.* 159: 247, 1949.
143. Richter, D. and R. M. C. Dawson. *J. Biol. Chem.* 176: 1199, 1948.
144. Richter, D. and R. M. C. Dawson. *Am. J. Physiol.* 154: 73, 1948.
145. Rinkel, M., H. J. DeShon, R. W. Hyde and H. C. Solomon. *Am. J. Psychiat.* 108: 572, 1952.
146. Roberts, E. and S. Frankel. *J. Biol. Chem.* 187: 55, 1950.
147. Roberts, E. and S. Frankel. *J. Biol. Chem.* 188: 789, 1951.
148. Roberts, E. and S. Frankel. *J. Biol. Chem.* 190: 505, 1951.
149. Roberts, E., F. Younger and S. Frankel. *J. Biol. Chem.* 191: 277, 1951.
150. Rosomoff, H. L. and D. A. Holaday. *Am. J. Physiol.* 179: 85, 1954.
151. Rossen, R., H. Kabat and J. P. Anderson. *A. M. A. Arch. Neurol. & Psychiat.* 50: 510, 1943.
152. Sacks, W. *J. Appl. Physiol.* 10: 37, 1957.
153. Scheinberg, P. *J. Clin. Invest.* 29: 1010, 1950.
154. Scheinberg, P. *Blood* 6: 213, 1951.
155. Scheinberg, P. *Neurology* 4: 101, 1954.
156. Scheinberg, P., L. I. Blackburn, S. C. Kaim and C. A. Stenger. *A. M. A. Arch. Neurol. & Psychiat.* 70: 260, 1953.
157. Scheinberg, P., I. Blackburn, M. Rich and M. Saslaw. *A. M. A. Arch. Neurol. & Psychiat.* 70: 77, 1953.
158. Scheinberg, P. and E. A. Stead. *J. Clin. Invest.* 28: 1163, 1949.
159. Scheinberg, P., E. A. Stead, E. S. Brannon and J. V. Warren. *J. Clin. Invest.* 29: 1139, 1950.
160. Schieve, J. F., P. Scheinberg and W. P. Wilson. *J. Clin. Invest.* 30: 1527, 1951.
161. Schieve, J. F. and W. P. Wilson. *Am. J. Med.* 15: 171, 1953.
162. Schmidt, C. F., S. S. Kety and H. H. Pennes. *Am. J. Physiol.* 143: 33, 1945.
163. Schneider, R. and H. Droller. *Quart. J. Exper. Physiol.* 28: 323, 1938.
164. Schwerin, P., S. P. Bessman and H. Waelsch. *J. Biol. Chem.* 184: 37, 1950.
165. Sensenbach, W., L. Madison, S. Eisenberg and L. Ochs. *J. Clin. Invest.* 33: 1434, 1954.
166. Sensenbach, W., L. Madison and L. Ochs. *J. Clin. Invest.* 32: 226, 1953.
167. Sensenbach, W., L. Madison and L. Ochs. *J. Clin. Invest.* 32: 372, 1953.
168. Shenkin, H. A., M. H. Harmel and S. S. Kety. *A. M. A. Arch. Neurol. & Psychiat.* 60: 240, 1948.
169. Shenkin, H. A., P. Novack, B. Goluboff, A. M. Soffe and L. Bortin. *J. Clin. Invest.* 32: 459, 1953.
170. Shenkin, H. A., R. B. Woodford, F. A. Freyhan and S. S. Kety. *A. Res. Nerv. & Ment. Dis., Proc.* 27: 823, 1947.
171. Snyderman, S. E., L. E. Hoit, R. Carretero and K. Jacobs. *Fed. Proc.* 9: 371, 1950.

172. Snyderman, S. E., L. E. Holt, R. Carretero and K. Jacobs. *Am. J. Clin. Nutrition* 1: 200, 1953.
173. Sokoloff, L. In: *Progress in Neurobiology. I. Neurochemistry*, edited by S. R. Korey and J. I. Nurnberger. New York: Hoeber-Harper, 1956, p. 216.
174. Sokoloff, L. In: *New Research Techniques of Neuroanatomy*, edited by W. F. Windle. Springfield: Thomas, 1957, p. 51.
175. Sokoloff, L. In: *The Process of Aging in the Nervous System*, edited by J. E. Birren, H. A. Imus and W. F. Windle. Springfield: Thomas, 1959.
176. Sokoloff, L., W. M. Landau, W. H. Freygang, L. P. Rowland and S. S. Kety. *Fed. Proc.* 14: 142, 1955.
177. Sokoloff, L., R. Mangold, R. L. Wechsler, C. Kennedy and S. S. Kety. *J. Clin. Invest.* 34: 1101, 1955.
178. Sokoloff, L., S. Perlin, C. Kornetsky and S. S. Kety. *Ann. New York Acad. Sc.* 66: 468, 1957.
179. Sokoloff, L., R. L. Wechsler, R. Mangold, K. Balls and S. S. Kety. *J. Clin. Invest.* 32: 202, 1953.
180. Stadie, W. C. *XIX Internat. Physiol Congr. Proc.* 24, 1953.
181. Stoll, W. A. *Schweiz. Arch. Neurol. u. Psychiat.* 60: 279, 1947.
182. Stone, W. E. *J. Biol. Chem.* 135: 43, 1940.
183. Stone, W. E. *J. Biol. Chem.* 149: 29, 1943.
184. Tower, D. B. *XIX Internat. Physiol. Congr., Proc.* 834, 1953.
185. Tower, D. B. *Neurology* 5: 113, 1955.
186. Tower, D. B. *Am. J. Clin. Nutrition* 4: 329, 1956.
187. Tower, D. B. and K. A. C. Elliott. *J. Appl. Physiol.* 4: 669, 1952.
188. Tower, D. B. and K. A. C. Elliott. *J. Appl. Physiol.* 5: 373, 1953
189. Traeger, H. S., G. J. Gabuzda, A. N. Ballou and C. S. Davidson. *Metabolism* 3: 99, 1954.
190. Tschirgi, R. D., R. W. Gerard, H. Jenerick, L. L. Boyarsky and J. Z. Hearon. *Fed. Proc.* 8: 166, 1949.
191. Viscontini, M., C. Ebnöther and P. Karrer. *Helvet. chim. acta* 34: 1834, 1951.
192. Wechsler, R. L., W. Crum and J. L. A. Roth. *Clin. Res. Proc.* 2: 74, 1954.
193. Wechsler, R. L., R. D. Dripps and S. S. Kety. *Anesthesiology* 12: 308, 1951.
194. Weil-Malherbe, H. *Biochem. Soc. Sympos.* 8: 16, 1952.
195. Weil-Malherbe, H. *J. Ment. Sc.* 98: 565, 1952.
196. Wilson, W. P., J. F. Schieve and P. Scheinberg. *A. M. A. Arch. Neurol. & Psychiat.* 68: 651, 1952.
197. Wingo, W. J. and J. Awapara. *J. Biol. Chem.* 187: 267, 1950.
198. Wortis, J., K. M. Bowman and W. Goldfarb. *Am. J. Psychiat.* 97: 553, 1940.
199. Wortis, J., K. M. Bowman, W. Goldfarb, J. F. Fazekas and H. E. Himwich. *J. Neurophysiol.* 4: 243, 1941.

CHAPTER LXXVIII

# Chemical environment of the central nervous system

ROBERT D. TSCHIRGI

*Departments of Physiology and Anatomy, University of California School of Medicine, Los Angeles, California*

CHAPTER CONTENTS



THE FUNCTIONAL CAPACITY of every neuron within the nervous system is dependent upon the nature of the milieu which invests it. Minute changes in chemical or physical parameters of this microenvironment will alter the threshold of excitability in adjacent cell membranes and thereby influence functional activity. Not only is the maintenance of proper metabolite concentrations of critical importance but the 'atmosphere' of organic and inorganic ions must be regulated within very narrow limits, for the phenomenon of excitability displays exquisite sensitivity to changes in electrolyte milieu. Since the commodity of the nervous system is information, meaningless fluctuations in significant components of the neuronal environment will introduce noise, in the communications sense, and it is not surprising, therefore, to discover unique homeostatic mechanisms designed to buffer the central nervous system against such changes and thereby achieve a maximum signal to noise ratio. On the other hand, controlled alterations of the central environment may also represent meaningful signals as, for example, the response of the respiratory center to changes in $[H^+]$, the temperature regulating centers to changes in local temperature, and the less well-defined influence of hormonal and metabolite concentrations on integrated central nervous activity. For this reason, it is important to consider the internal microenvironment of the central nervous systems not as a primordial sea of elaborately guarded constancy but as a dynamic mechanism within the machinery of nervous activity whose changing pattern of inhomogeneities modifies and regulates behavior.

## THE MICROENVIRONMENT

### *Relation of Cerebrospinal Fluid to the Microenvironment*

Until recently, the basic anatomy of the central nervous system microenvironment did not seem to propose any considerable difficulties. As with other tissues, a continuous fluid phase, the interstitial compartment, was believed to exist outside of all cell membranes and to be separated from the plasma by the endothelial wall of the capillaries. A shell of this fluid enveloping a cellular element comprised the microenvironment of that element, and all exchange

between the interior of cells and the blood plasma was thought to occur through this fluid by passive diffusion and convection. In order to prevent the neurons from idly drifting about in this sea of interstitial fluid, the neuroglia were believed to function as a sponge-like skeleton within whose interstices the neurons are caught and the whole central nervous system thus provided with some degree of mechanical rigidity. Although the physiologist seldom allows himself to be restricted by anatomical considerations, the histological picture obtained by light microscopy did appear to provide evidence for this elegantly simple scheme. Extracellular spaces abounded throughout the sections of central nervous tissue and were dutifully named after their originators as spaces of His, spaces of Held, etc. Elaborate 'pseudo-lymphatic' systems were described by which perineuronal spaces became continuous with perivascular spaces opening ultimately into the subarachnoid space (160, 161). Through these channels cerebrospinal fluid was conjectured to flow, propelled by the pulsations of the blood vessels, perhaps to and fro or perhaps only in one direction. Many authors envisioned these spaces as comprising a microsewage disposal system emptying finally into the subarachnoid cesspool whence the digested residues of neuronal metabolism flowed sluggishly back into the blood stream. Some considered them the rivers of abundance down which streamed, from the cornucopia of the cerebrospinal fluid, all the nutrients and other requirements of the neurons. Still others saw them as highways of commerce with barges of glucose destined for the furnaces of neuronal metabolism passing garbage scows of refuse headed in the opposite direction. In any case, there appeared to be a continuous and open pathway between the unique and mysterious cerebrospinal fluid and the functional units of the central nervous system, giving rise to the concept that the cerebrospinal fluid was, indeed, the internal milieu. In the 1920's, Stern and her collaborators developed a simplified concept which was notable for its graphic imagery and lack of experimental verification (141). They conceived of the cerebrospinal fluid, expressed through the 'barrière hémato-encephalique' into the cerebral ventricles, as percolating centrifugally through the extracellular interstices of the nervous tissue like an animated coffee pot, supplying the brain with electrolytes en route. In 1926 Hauptmann generalized this function (65) and declared that the cerebrospinal fluid acts as an intermediary between plasma and brain for the entire metabolic needs of that tissue. In 1933, Spatz introduced a bold antagonistic note by postulating that the penetration of the brain by dyes from the cerebrospinal fluid is strictly a process of passive diffusion without convection and that the brain behaves in this respect like a homogeneous colloidal mass which contains no free fluid (137). Soon thereafter, the concept of the cerebrospinal fluid as the *milieu interne* of the central nervous system fell into disrepute and this mystic liquor, which for centuries had been thought to contain the highest and most refined essence of life, was relegated to the role of a water bath protecting the submerged brain from external injury.

The concept of an inward perivascular flow of cerebrospinal fluid was recently revived by Sacks & Culbreth (132) to explain the penetration into the brain of the radioactive tracer $P^{32}$; and Brierley (19), unlike most previous investigators, demonstrated india ink particles in the perivascular spaces of the central nervous system following their injection into the cisterna magna, from which he implicated the centripetal perivascular flow in transmission of infective agents from the cerebrospinal fluid into the brain. It has been suggested by Bakay (9, p. 61) that Brierley's results with india ink might have been caused by an artificial flow in the perivascular system as a consequence of the rapid exsanguination used to dispatch the experimental animals. Patek (122) was unable to detect a perivascular circulation of cerebrospinal fluid under normal conditions, in agreement with the older literature (134, 160), but was able to fill the perivascular spaces with india ink and colloidal mercury sulfide, administered intrathecally, by simultaneously dehydrating the brain with intravenous hypertonic sodium chloride. No perivascular accumulation of intrathecal colloidal material occurred in the absence of such dehydration. Recent studies by Bertrand (15) on the diffusion and absorption within the brain of intracerebrally administered prussian blue and india ink led that author to conclude that the transit of material along perivascular spaces is of minor importance. Bakay (9) agrees with this conclusion and considers that there is no reason to believe that an intrathecal isotope follows any particular pathway of absorption into the brain.

### *Functional Anatomy of Fluid Compartments*

But the intercellular spaces remained, and the physiologist filled them with a solution derived from the plasma by ultrafiltration which, if not cerebrospinal fluid, was of similar composition. Since no technique was available to obtain and analyze inter-

stitial fluid directly from central nervous tissue, it was assumed to resemble extracellular fluid of other tissues and to be the primary, if not exclusive reservoir for the 'extracellular' ions, $Na^+$ and $Cl^-$. Using these two assumptions, the approximate volume of the interstitial space could be calculated by analyzing central nervous tissue for $Na^+$ or $Cl^-$ and computing the volume of solution represented by each ion in the concentration predicted by the Gibbs-Donnan equilibrium for an ultrafiltrate of plasma. Brain contains about 35 mEq of $Cl^-$ per kg and about 57 mEq of $Na^+$ per kg. If we consider the concentration of $Cl^-$ in the cerebrospinal fluid—which at equilibrium closely resembles plasma ultrafiltrate—to represent the concentration of that ion in the interstitial fluid, then the volume of extracellular water is about 30 per cent of the brain wet weight. This figure is similar to that calculated for liver, and nearly twice that in muscle (109). However, a similar calculation using the figures for $[Na^+]$ instead of $[Cl^-]$ reveals a significantly larger space (approximately 35 per cent), and it is necessary to conclude that either the $Cl^-$ concentration in the interstitial fluid is less than assumed, or that some of the brain $Na^+$ is intracellular. For reasons which are as much articles of faith as logical necessities, it is generally agreed that the latter is more probable. In general, the $Cl^-$ of vertebrate nerves behaves as if it were extracellularly situated (5), and brain slices appear to be relatively impermeable to both sodium and chloride (35). Although the rate of equilibration of intravenous $Na^+$ and $Cl^-$ with central nervous tissue is much slower than with other tissues (see the discussion of the blood-brain barrier below), the $Na^+$ and $Cl^-$ of brain *in vivo* do respond as extracellular ions to plasma changes when a sufficiently long period of time is allowed for these changes to be reflected in the central nervous system (167, 169). Flexner & Flexner (42) have shown that the chloride concentration of the developing guinea pig cerebral cortex decreases by 40 per cent between the fortieth day of gestation and term. During this same period, the concentration of sodium decreases by only a fraction of this amount. These workers conclude that, during this period of functional onset within the developing central nervous system, sodium has become an intracellular constituent of at least some central structures.

Values ranging between 25 per cent and 40 per cent (38) for interstitial space in the central nervous system have been widely quoted in the literature and depend primarily on the assumptions mentioned previously. Whether the concentration of the 'extracellular' ion in the interstitial fluid is assumed to be equal to its concentration in the plasma, an ultrafiltrate of plasma or the cerebrospinal fluid, does not markedly alter this figure.

Woodbury (167) has approached the question of central nervous system fluid compartments through a careful analysis of rates of accumulation in the central nervous system of various radiotracer inorganic ions. He first determined that brain chloride is in complete equilibrium with plasma by decreasing plasma chloride concentration with intraperitoneal injections of isomolar glucose solutions and determining brain chloride concentration. The per cent change in brain chloride equaled the per cent change in plasma chloride for as much as 30 per cent decrease. Similarly, increasing plasma chloride with 20 mEq per kg of NaCl intraperitoneally increased brain chloride proportionately. On this basis, the author assumes that brain chloride is distributed only in the extracellular fluid and that the chloride space is an adequate measure of the total extracellular volume in brain.

Using the equations developed by Solomon (136), Woodbury has determined that the curve for uptake of radiochloride by the brain of rats can be resolved into two components; one with a half time of 65 min. and the other with a half time of 25 hr. Radiosulfate ($S^{35}O_4$), on the other hand, equilibrates with only 3.9 per cent of the total brain volume during the first 16 hr. after intraperitoneal administration. Subsequently the sulfate space appears to increase, but this is attributed to 'binding' of the sulfate by the tissues. Before this 'binding' process occurs, the rate of uptake of sulfate can be resolved into a single component with a half time of 80 min., which is believed to correspond to the rapid component of the chloride uptake curve. The curve for uptake of radiosodium resolves into three components, two with half times of 90 min. and 23 hr. corresponding to the two chloride components, and a third with a half time of 13 min. This latter component is similar to a fast component in the uptake of potassium, and is therefore postulated to represent movement into the intracellular compartment.

From these results, Woodbury proposes that the interstitial volume of the central nervous system, represented by the chloride space (25 per cent of the brain total water), is composed of two 'phases,' a rapid phase (4 per cent) into which sulfate movement is restricted and a slow phase (21 per cent) which can be entered from the rapid phase by some solutes, such as $Cl^-$. In addition, the intracellular compart-

ment and the cerebrospinal fluid are postulated to exchange with the rapid phase of the interstitial compartment. These relationships are summarized in figure 1 (167, fig. 38) which attributes the slow phase of the interstitial compartment to the glia, which the author apparently considers to be extracellular. However, electronmicrographic studies (see below) do not support this concept of an extracellular 'glue' occupying over 20 per cent of the brain volume, and if, indeed, the slow phase does represent penetration into neuroglia, it must be considered as part of cell permeability. It is interesting to note that the volume of the 'true' morphologic extracellular space of rat cortex has been estimated from electronmicrographs as approximately 4 per cent.

For the electrophysiologist, the existence of an extracellular continuous phase of conducting fluid surrounding the membranes of cellular elements has been the foundation of his theoretical interpretations. As his microelectrode descends, micron by micron through cortical tissue, he visualizes the tip passing into a lacuna of interstitial fluid through which currents generated by adjacent neurons are flowing. As the height and form of the oscilloscope tracing change, he envisions the electrode approaching a cell membrane and then, with an electrical snap, penetrating to the interior. Thus, the electrical resistance

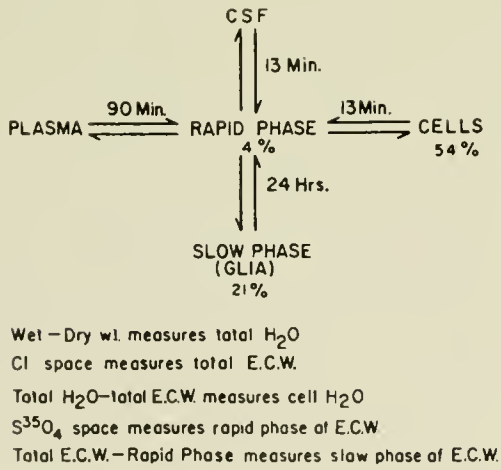



FIG. 1. Woodbury's concept of the various fluid compartments in the cerebral cortex. Time indicated on the *arrows* is the half time for equilibration of a solute across that particular phase boundary. The *figure* under each phase is the percentage of total water in that phase. *E.C.W.*, extracellular water; *CSF*, cerebrospinal fluid. A possible route of transfer of materials from plasma directly to cerebrospinal fluid is not indicated on this diagram. [From Woodbury (167).]

of central nervous tissue has also been interpreted to require a sizeable volume of interstitial fluid in the belief that "the brain consists of cells and fibers surrounded by relatively high resistance membranes, which are embedded in an intercellular mass of relatively high specific conductivity" (151).

Attempts to utilize foreign substances, which equilibrate rapidly between blood and interstitial fluid but do not penetrate cells, have been relatively unsuccessful for estimating central nervous system extracellular space. Inulin, with its high molecular weight, lipoid insolubility, low osmotic activity in readily detectable concentrations and lack of toxicity, has been widely used for determining total body extracellular space or, by use of tissue samples, for specific organs. Other substances which have compared favorably with inulin include ferrocyanide, radioactive sulfate and thiosulfate. When administered *in vivo*, however, these substances are effectively blocked from entry into the brain and cerebrospinal fluid by the blood-brain barrier, and are therefore unsuitable for determining the extracellular volume of the intact central nervous system. In an effort to surmount these difficulties, Allen (3) utilized an *in vitro* diffusion technique with slices of rat brain incubated in appropriate media containing inulin or ferrocyanide which had been shown by Weed (160) not to penetrate the living cells of nerve tissue. After determining the amount of tissue swelling which had occurred, the ferrocyanide (or inulin) space was calculated as ml per 100 gm of tissue by the following formula:

$$\text{ferrocyanide space (ml / 100 gm)} = \frac{\text{ferrocyanide in tissue (mg / gm)}}{\text{ferrocyanide in medium (mg / ml)}} \times 100$$

Following an initial period of rapid diffusion of the ferrocyanide or inulin into the tissue slice, a slower and linear increase in volume of the space continued for 2 hr., due most likely to the gradual penetration of the material into the cells. Extrapolation of this phase of the curve to zero time indicated an extracellular space for rat cerebrum of 17 per cent using ferrocyanide and 14.5 per cent using inulin. Determination of chloride space in similar tissue slices at zero time, assuming equilibration with cerebrospinal fluid chloride, averaged 31 per cent, which is comparable to that reported by others and almost twice as large as the inulin-ferrocyanide space.

If the tissue fluid of rat brain is assumed to be identi-

cal with cerebrospinal fluid insofar as electrolyte composition is concerned, and if the extracellular volume is approximately 16 per cent, then there must be an appreciable quantity of both chloride and sodium in the intracellular compartment. This conclusion was also entertained by Mancry *et al.* (110, 111) in their extensive studies upon equilibration of radioactive chloride and sodium in various tissues. Amberson and co-workers (5) produced evidence that a large fraction of brain chloride did not vary proportionately to serum chloride; hence it was to be considered nondiffusable. Furthermore, the direct analysis of axoplasm from giant axon of squid by Hodgkin (81) has clearly revealed that sodium and chloride exist intracellularly and in concentration ratios to outside medium of 1 : 9 and 1 : 14, respectively.

Despite the careful controls used by Allen in determining the inulin-ferrocyanide space, the results of *in vitro* techniques must be approached with considerable caution. For example, if a rapid redistribution of water from the interstitial compartment into the intracellular were to occur in these isolated tissue slices before the diffusion measurements were completed, a spuriously small extracellular volume would result. That such a shift may occur has been proposed by van Harreveld & Ochs (151) who found that the *in vivo* cerebral cortex of rabbits develops a rapid increase in electrical resistance within 5 min. after circulatory arrest. They attribute this increase to asphyxial changes in cellular membranes which allow sodium and chloride to enter the cell accompanied by interstitial water, thus reducing the volume of the extracellular compartment. Further evidence for marked and rapid changes in ionic, and presumably water, distribution in slices of cerebral tissue has been presented by Krebs *et al.* (97) with their demonstration that brain slices lose about 40 per cent of their potassium content within a few minutes after being suspended in an incubating medium. It is therefore quite possible that significant irreversible changes in the relative volumes of cerebral tissue fluid compartments may occur during the 10 min. required to remove the brain, prepare the slices and immerse them in the medium.

Perhaps the most serious dissension to the concept of 30 per cent or even 15 per cent extracellular volume in central nervous tissue arises from the electronmicrographs of osmic-acid fixed sections. In a recent paper, from which figure 2 is taken, Schultz *et al.* (135) present this view most emphatically.

"In electronmicrographs of well-preserved cortex the close apposition of cells and their processes is of particular interest. It is particularly evident at high magnification . . . that there are absolutely no large-scale extracellular gaps or spaces present, as Dempsey & Wislocki (30) and Farquhar & Hartmann (39) pointed out. Where one cytoplasmic mass abuts against another there are fairly constant gaps of

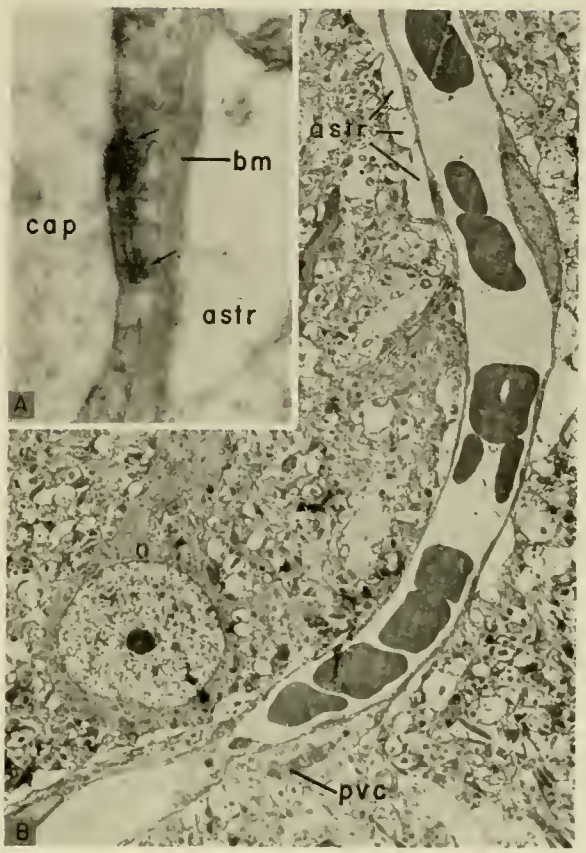



FIG. 2. Electronmicrographs of adult rat cerebral cortex preserved with buffered osmium textroxide. *A:* The lateral junction between two adjacent endothelial cells at high magnification. The lumen of the vessel (*cap*) is to the *left*; astrocytic cytoplasm (*astr*) is to the *right*. The endothelium rests on a basement membrane (*bm*). The endothelial margins overlap slightly, the lapping here amounting to 330 mμ. Structures resembling adhesion plates are present at the beginning and end of the overlap as indicated by the *arrows*. × 45,000. *B:* A longitudinal section of a capillary. The astrocytic sheath is incomplete, but of the elements abutting on the capillary wall, astrocytic perivascular processes (*astr*) are far in the majority. The wall of this vessel consists of a one cell thick layer of endothelium for much of its course, but portions of a flattened perivascular cell (*pvc*) may be seen in the *lower part* of the figure. These cells may be rudimentary smooth muscle. A large neuron (*n*) is immediately *below the inset*. Note the almost complete absence of interstitial space. × 2,250. [From Maynard *et al.* (114).]

about 200 Å between osmiophilic lines. While no doubt this is a potential space and probably serves as a diffusion route, it is exactly the sort of space that one finds between epithelial cells in general. In an epithelium one thinks of this as a 'cement layer' binding adjacent cells together. It is reasonable to think that it may play a similar role in the nervous tissue. The only extracellular gaps which are wider than this are small pockets formed where the membranes of adjacent cells diverge one from the other. . . .

"For the above considerations we derive a picture of nervous tissue that is rather different from what the light microscopist often imagines. Essentially all of the space is filled with living cell processes of one sort or another. It is likely that these processes are more or less fastened one to another, but there is no other extracellular means for support. The special technical methods developed for neurocytological investigations with the light microscope unfortunately often produce serious shrinkage artefact which creates spaces where none existed originally."

So we are faced with the mystery of the disappearing interstitial volume and, as yet, no satisfactory explanation is available to unite these disparate data. The physiologist finds comfort in dismissing the electronmicrographs as artefacts bearing unknown relationship to the *in vivo* situation, but this attitude has the familiar ring of the pot calling the kettle black. If we accept the electronmicrographs at face value, then considerable revision of current concepts concerning the nature of cell membranes and the composition of the intracellular compartment is required.

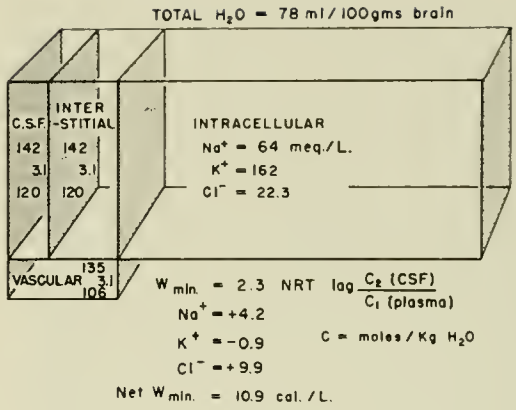



FIG. 3. Diagram of the fluid compartments of the central nervous system. Size of each rectangle is proportional to estimated volume of the compartment it represents. Concentrations of $Na^+$, $K^+$ and $Cl^-$ in cerebrospinal fluid (*CSF*) as well as calculations for $W_{min.}$ are from Flexner (41). Intracellular concentrations calculated on the basis of 15% interstitial volume.

*Composition of Interstitial Fluid*

Figure 3 illustrates the interrelationships of the water compartments of the central nervous system and provides an estimate of their relative volumes. The interstitial compartment is shown as comprising approximately 15 per cent of the total water, although, as discussed above, this figure is problematical. The composition of the interstitial fluid with respect to $[Na^+]$, $[K^+]$ and $[Cl^-]$ is proposed to be essentially the same, on the average, as the cerebrospinal fluid, although no direct measurements of central nervous system interstitial fluid have been made. However, the ingenious experiments of Wallace & Brodie (157, 158) tend to substantiate this position. These authors administered sodium or potassium salts of iodide, thiocyanate and bromide to dogs, and determined the ratios of these ions to the normally present chloride in the plasma and in the tissues. In all tissues examined except the brain, the three anions were distributed in the same ratio to chloride as in the plasma. In the central nervous system, however, the anion to chloride ratio was the same as in the cerebrospinal fluid, and this ratio was considerably smaller than that found in the plasma. From these results they concluded that iodide, thiocyanate, bromide and chloride are distributed in the interstitial water of the central nervous system in ionic equilibrium not with plasma, but with cerebrospinal fluid, and that the composition of the interstitial fluid is the same as the cerebrospinal fluid.

Olsen & Rudolph (120) studied the transfer of radioactive sodium ($Na^{24}$) and radioactive bromide ($Br^{82}$) ions between blood, cerebrospinal fluid and brain tissue. The entry of the ions into cerebrospinal fluid after intravenous injection followed a single exponential with rates of the two ions of the same order. The ions equilibrated slowly between cerebrospinal fluid and serum, and rapidly between skeletal muscle and serum, irrespective of the mode of administration. However, equilibrium between brain tissue and cerebrospinal fluid was rapid following intravenous injection, but slow after intracisternal injections due to the long diffusion distances to the interior of the brain. These data indicate that the intercellular fluid of nervous tissue is in equilibrium with cerebrospinal fluid and not serum, and that the formation of central nervous system interstitial

fluid is similar to the formation of cerebrospinal fluid.

Relatively unimpeded exchange between the cerebrospinal fluid and adjacent central nervous system tissue has been demonstrated for a variety of radioisotopes of inorganic ions, as well as other solutes in the cerebrospinal fluid (9). Bakey (9) injected colloidal and diffusible dyes (both acidic and basic) of known particle size into the subarachnoid spaces, and concluded that any barrier between cerebrospinal fluid and central nervous system tissue must have a pore size of at least 20 Å in diameter. Similar conclusions were presented by Tschirgi (146) on the basis of the observation that trypan blue dissolved in plasma did not stain the brain of anesthetized animals even after several hours of application to the cortical pial surface, although the surrounding dura, fascia and muscle which came into contact with the dye-plasma solution were deeply colored. Contrariwise, trypan blue dissolved in buffered saline rapidly diffused into the underlying cortical parenchyma. When the superficial pia-glia membrane was damaged by a slight tear, then the plasma-dye solution readily stained the brain tissue in the area of the defect. Using Bennhold's gelatin diffusion technique for determining the relative amounts of protein-bound and unbound dye present in the solution, it was found that the amount of stain which diffused into the uninjured brain, following topical application of purified plasma albumin-dye solutions, was directly related to the amount of unbound dye present and to the duration of application. Furthermore, the phenomenon could be quite accurately duplicated by a physical system consisting of white opaque gelatin (to represent brain tissue) separated from the various protein-dye solutions by a protein-impermeable 'viskin' membrane. Anatomically, this barrier to protein diffusion from the cerebrospinal fluid would appear to be composed of the superficial pia-glia membrane (fig. 4). The ependymal lining of the ventricular walls does not seem to impose a significantly greater barrier to the diffusion of inorganic ions from the ventricular cerebrospinal fluid into brain tissue (fig. 4).

Therefore, on the basis of currently available evidence, it is justified to consider the cerebrospinal fluid as an expanded lacuna of the interstitial fluid compartment, and to consider the neuronal functional consequences of cerebrospinal fluid composition as reflecting with some accuracy the state of the cellular milieu.

## THE BLOOD-BRAIN BARRIER

The question of secretion versus ultrafiltration as the mechanism of formation of cerebrospinal fluid has received considerable attention in the literature. This topic is reviewed in Chapter LXXII in this *Handbook* and also by Katzenelbogen (88). Insofar as the interstitial fluid of the central nervous system has the same composition as the cerebrospinal fluid, the same question concerning the mechanism of formation must pertain. Flexner (41) has attempted to calculate the thermodynamic work required to manufacture a liter of cerebrospinal fluid from a theoretically infinite reservoir of blood plasma. The greatest amount of positive work is needed to account for the relatively higher concentration of sodium and chloride ions in cerebrospinal fluid than in blood plasma. After considering the theoretical Donnan distribution, which would be expected in an ultrafiltrate, and after subtracting the hydrodynamic energy available from the blood pressure, Flexner arrives at an estimated 10.9 cal. per l. of cerebrospinal fluid which must be provided by the mechanism responsible for the formation of that fluid. Figure 3 gives these data only for $[Na^+]$, $[K^+]$ and $[Cl^-]$, although the estimate for total $W_{min}$ is based on a consideration of all of the significant constituents of cerebrospinal fluid.

If the interstitial fluid averages the same composition as the cerebrospinal fluid, then these same thermodynamic considerations must be applied to the formation of the neuronal milieu. Since there is abundant evidence to indicate that the interstitial fluid is not formed by an inward bulk movement of cerebrospinal fluid, but, rather, that the subarachnoid cerebrospinal fluid is formed, in part, by a centrifugal flow of interstitial fluid out of the central nervous system (see Chapter LXXII by Davson on cerebrospinal fluid in this *Handbook*), then it is necessary to hypothesize some structure coextensive with most of the vasculature of the central nervous system which regulates solute movement and in some aspects actively transports solutes between the plasma and the interstitial fluid.

The earliest report of this singular 'barrier' between blood plasma and the extravascular fluids of the central nervous system was the discovery by Ehrlich (34) in 1885 that intravenous injection of the acidic dye, coerulein-s, stained most organs in his experimental animals, but left the central nervous system relatively uncolored. Subsequently, Roux & Borell (129) in 1898 demonstrated that tetanus toxin was

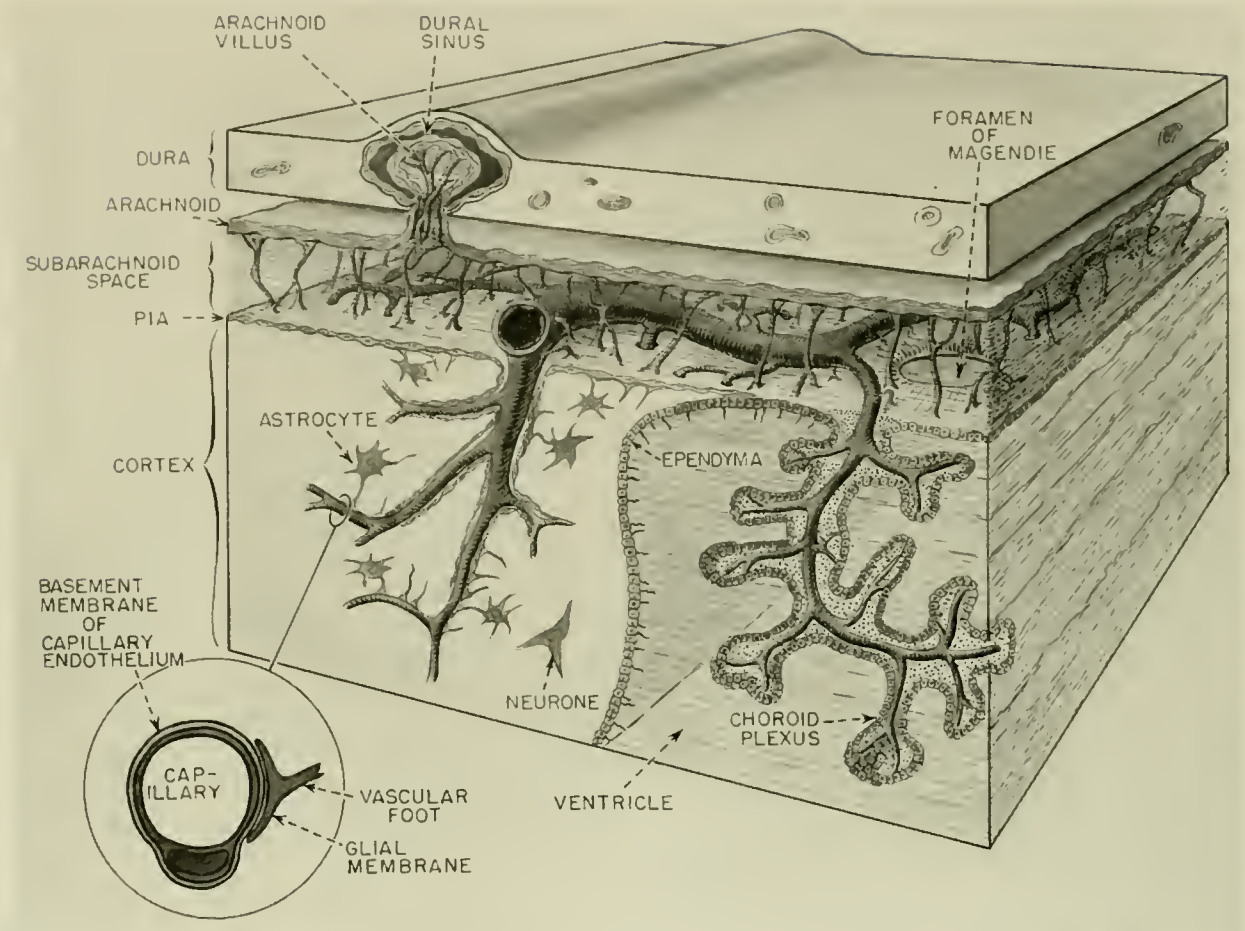



Fig. 4. Semidiagrammatic section of central nervous system and investing membranes, illustrating relationships of various fluid compartments and barriers. *Enlargement at lower left* illustrates three probable sites of blood-brain barrier action; capillary endothelium, basement membrane and perivascular glia. Note that invaginating pia does not accompany penetrating vessels beyond larger branches. Astrocytes form an 85–90% complete sheath around blood vessels, although only a few are illustrated. [Redrawn from Spatz (137).]

ineffective when injected intravenously in doses 10 times those which produced marked symptoms after intrathecal administration. Biedl & Kraus (16) in 1898 and Lewandowsky (103) in 1900 showed similar phenomena for bile and sodium ferricyanide, respectively.

The classic experiments of this genre were conducted by Goldmann (55) from 1908 to 1913 using the acid, semicolloidal dye trypan blue which has since come to be regarded as the prototype of stains that, in general, color the central nervous system only after intrathecal injection.

In his 'first experiment,' Goldmann demonstrated that, following intravenous injection, vital staining occurred in all tissues of the organism except the brain which remained colorless with the notable exception of the choroid plexuses. He observed no toxic symptoms in these animals; but following intrathecal administration of the dye ('second experiment'), the brain was stained deep blue, especially adjacent to those subarachnoid areas into which the dye had been introduced, and the animals developed seizures and paralysis. He was led to the erroneous conclusion that the seat of all blood-brain barrier activity was the choroid plexus, and he expanded this concept into the generalization that all substances must pass from the blood through the choroid plexus in order to enter the brain. The subsequent vicissitudes of that concept have been briefly described above.

Walter (159) in 1929 concluded in a comprehensive

review that the results of vital dye studies could not be explained without hypothesizing three distinct barriers: the blood-brain barrier coextensive with the cerebral vasculature, the blood-cerebrospinal fluid barrier located presumably in the choroid plexuses, and the cerebrospinal fluid-brain barrier which has been mentioned earlier in this chapter (fig. 4). Despite the evidence for assuming considerable similarity between cerebrospinal fluid and central nervous system interstitial fluid, various reasons have been marshalled to differentiate functionally between the blood-brain and the blood-cerebrospinal fluid barriers. After intravenous administration, some drugs have been shown to exert their pharmacologic action on the central nervous system before they reach detectable concentrations in the cerebrospinal fluid. This does not necessarily imply a uniquely different mechanism involved in these two barriers, since the observation can be explained by assuming that the local perineuronal concentration of the drug achieves pharmacological levels by passage from adjacent capillaries before sufficient material to be detected has entered the large cerebrospinal fluid reservoir. However, it does imply that the drug need not pass into the cerebrospinal fluid before reaching the neuronal milieu.

Of greater significance in suggesting a difference between the blood-brain barrier mechanism and blood-cerebrospinal fluid mechanism is the statement by Friedmann & Elkeles (45) that the barriers react differently to the electric charge of various vital dyes. According to these authors, the blood-cerebrospinal fluid barrier is more permeable to acidic (negatively charged) dyes, whereas the blood-brain barrier is more permeable to basic (positively charged) dyes. In general, conclusions from vital dye studies concerning the blood-extravascular barriers of the central nervous system are tenuous at best. Even if plasma levels of the dyes are carefully controlled and equated on a molar basis, still it is virtually impossible to conclude from visual inspection alone that more or less dye has penetrated to the intercellular fluid of the central nervous system simply because the tissue is grossly or microscopically more or less colored than with equimolar blood concentrations of other dyes. The final coloration will depend not only on the amount of dye present in the interstitial fluid, but upon the color intensity of the dye, upon the oxidation-reduction reactions which markedly affect the color of many dyes, upon methods of sample preparation for observation, and upon the penetration and accumulation of the dye within the intracellular compartment.

It has been suggested (146, p. 34) that the incontrovertible observation that, generally speaking, intravenous basic dyes do stain the central nervous system more readily than acidic ones may result from the greater propensity for plasma protein conjugation, at blood pH, by the acidic dyes, as shown by Bennhold some years ago (12). Thus the measure of blood-brain barrier impermeability with an acidic dye, such as trypan blue, may be largely a measure of blood-brain barrier impermeability to plasma proteins with which the dye is strongly associated.

The concept that the blood-cerebrospinal fluid barrier has significantly different permeability characteristics than the blood-brain barrier for metabolically significant solutes has been recently supported by Bakay (9). This author believes that, following intravenous injection of $P^{32}$ as inorganic phosphate, the bulk of the isotope arriving at the cerebral cortex uses the cerebrospinal fluid as intermediary. He bases this opinion on radioautographs of sectioned cat brains made shortly after intravenous injection of $P^{32}$, which show that the pattern of appearance of the isotope is identical with that in a brain injected intracisternally. The diffusion in both cases spreads from the surfaces in contact with the cerebrospinal fluid centripetally into the tissue. Following intravenous administration, the high initial concentration of $P^{32}$ in the periventricular layers, as compared with other areas, suggests to Bakay that a large portion of the plasma phosphate enters the cerebrospinal fluid through the choroid plexus. He concludes:

"A dualistic theory could serve as a working hypothesis to explain the diffusion of phosphates from the blood into the central nervous system. During the initial phase of absorption $P^{32}$ enters the brain via the cerebrospinal fluid after it has passed the blood-cerebrospinal fluid barrier. This phase is characterized by a large concentration of the tracer in the surface areas and a decline in activity of the cerebrospinal fluid. The pattern of diffusion is the same whether the tracer has been injected intravenously or intracisternally. The latter phase of absorption shows a slow and gradual increase of $P^{32}$ concentration in the entire brain, presumably due to a direct passage of the tracer through the blood-brain barrier by transcapillary exchange" (9).

Herlin (71) agrees with this general conclusion but emphasizes the slowness of movement of subarachnoid radioactive orthophosphate into the deeper regions of the central nervous system. He interprets the results of Bakay & Lindberg (10) and Lindberg & Ernster (105), who showed that 40 per cent of the $P^{32}$ in the

central nervous system was bound in organic complexes within 2 min. after injection into the cerebrospinal fluid, as indicating a metabolic barrier occurring in cell layers bordering the cerebrospinal fluid system. He believes that this barrier within the cerebrospinal fluid-brain boundary delays the transport of $P^{32}$ in such a way that the orthophosphate rapidly enters into organic compounds in the outer cell layers and may subsequently enter the deep structures of the brain by metabolic transportation as well as diffusion.

The ontogenetic maturation of the blood-brain barrier has occupied considerable attention and has recently been proposed as the explanation for the development of kernicterus in babies with erythroblastosis (78). Irrespective of the blood level of bile pigments in a jaundiced human adult, kernicterus rarely develops. On the other hand, Gröntoft (60) perfused human and animal fetuses with trypan blue and found the brain normally impermeable to this vital dye, even in human fetuses as early as the 5 cm stage. Grazer & Clemente (57) similarly found that the central nervous system of rat embryos from 10 days to birth is impermeable to trypan blue administered *in vivo*. They conclude that this impermeability in the developing central nervous system exists at the time when blood vessels invade the brain. They caution, however, that it cannot be assumed that the mechanisms which prevent protein-bound dyes from penetrating the cerebral blood vessels are the same for all other substances. Thus, with the application of radiotracers, significant changes in rates of penetration with age were observed. Fries & Chaikoff (46, 47) showed that the uptake of parenterally administered $P^{32}$ by liver, kidney, skeletal muscle and blood remained constant or increased as the animal matured, whereas uptake by the brain was greatly reduced. Similarly, Bakay (9) demonstrated that the permeability of rabbit brain to $P^{32}$ is greatest in early uterine life and continues to decrease until about 7 wk. of postnatal development. Despite the fact that the embryonic and early postnatal brain concentrates considerably more $P^{32}$ than does the adult brain, its uptake, as shown in figure 5, is still low when expressed in absolute values and compared with any of the other tissues (8). Bakay concludes that even in the fetus there exists a barrier for $P^{32}$ between blood and central nervous system, but the permeability of this barrier is greater than in adults.

In addition to certain of the investing membranes, there are several special structures within the central nervous system of adult animals which do become stained after parenteral injection of vital dyes or which readily accumulate blood-borne radiotracers. These include the pineal body, the pituitary gland, area postrema, subfornical organ, supraoptic crest and choroid plexuses. All of these regions are highly vascular, and many are known, or suspected, to have a secretory function. Borell & Örström (18) and Bakay (9) have studied this relative absence of blood-brain barrier activity with $P^{32}$ (fig. 6) which accumulates in the hypophysis in a fashion similar to its accumulation in the liver. Herlin (70) compared the effects of intraperitoneal versus intracisternal administration of $P^{32}$ in rabbits and obtained results completely in accordance with Goldmann's trypan blue experiments. After intraperitoneal injection, the tracer was concentrated in the choroid plexus but almost absent from the neighboring wall of the ventricle (fig. 4), whereas after intracisternal injection, $P^{32}$ was concentrated in the ventricular wall while the choroid plexus was almost free of radioactivity.

The area postrema consists of a loose stroma containing an abundance of sinusoidal vessels located in the fourth ventricle between the mid-line and the nucleus fasciculi gracilis. This structure has been observed to stain with intravenous vital dyes (164) and to accumulate $P^{32}$ (9) and $Br^{82}$ (61). These unique permeability characteristics have been proposed by Andrew & Taylor (6) to account for their observation that an area of special sensitivity to alterations of tonicity in the cerebrospinal fluid exists in the floor of the fourth ventricle, and by Clemente *et al.* (23) to

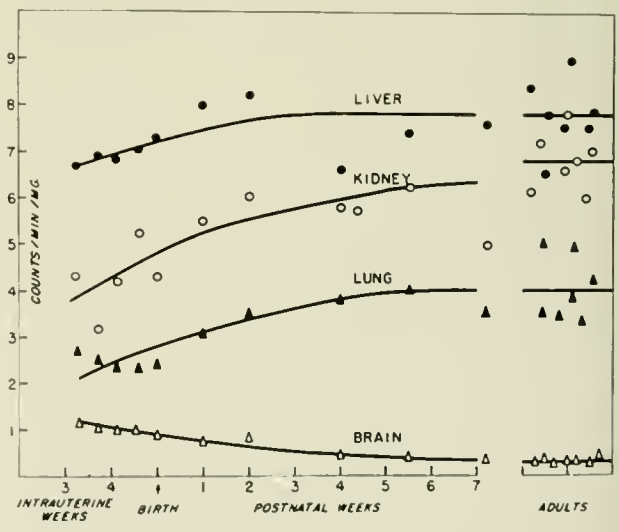



FIG. 5. $P^{32}$ concentration in various organs of fetal, young and adult rabbits 24 hr. after injection. [From Bakay (8).]

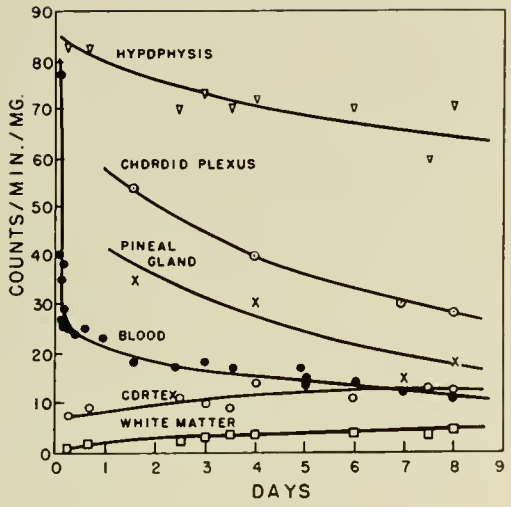



FIG. 6. $P^{32}$ concentration of various parts of the human brain following intravenous injection of 2 mc of the tracer per 70 kg of body weight. [From Bakay (9).]

account for the appearance of electrical spike activity in fiber tracts joining the area postrema and adjacent medulla following intravenous 3 M sodium chloride.

It may be concluded that for substances to reach the functional cellular elements of most of the central nervous system from the blood stream, they must pass through one or more 'barriers' which in some fashion regulate this intra-extravascular traffic. The biochemical machinery of these barriers is still obscure, but is clearly of major significance in understanding the control of the chemical environment of neurons. Krogh (98) has recently reintroduced the concept of lipoid solubility as a predominant factor in determining barrier permeability. This hypothesis, while quite satisfactory for some compounds, is, for example, unable to account for the rapid penetration of barbiturates (87) or for the relative penetration of a series of sulfonamides (56). The blood-brain penetration of these latter compounds is not related to lipoid solubility nor to molecular weight, but rather to their dissociation constants.

In general, however, there is considerable similarity between blood-brain barrier permeability and cell membrane permeability. It appears that for solutes to pass from the plasma to the intercellular fluid of the central nervous system (with the exceptions noted) they must, for the most part, pass through, not between cells. This barrier does not represent a simple sievelike impediment to otherwise free diffusion, but rather a distinct polarized secretory mechanism which governs the concentration of certain solutes in the intercellular fluid.

Despite the mass of data which has accumulated, the only generalizations that can be made remain phenomenological: ". . . that the blood-brain barrier (including the blood-cerebrospinal fluid barrier) is a mechanism for producing a peculiarity in the exchange of most substances between the plasma and the intercellular fluid of the central nervous system; that this peculiarity manifests itself as a decreased rather than an increased rate of exchange; and that this phenomenon is not localized to the choroid plexus, but is associated with the entire cerebral vasculature" (146).

### *Anatomy of the Blood-Brain Barrier*

The anatomy of this panvascular barrier has remained surprisingly elusive, but the claims and counterclaims have developed a fervor exceeding almost any other aspect of this subject. Following the early unsatisfactory choroid plexus hypothesis of Goldmann referred to previously, various anatomical sites were proposed which involved, among other structures, the meninges and the reticuloendothelial system (170). However, the polemic dispute resolved into two major camps, the perivascular glial membrane theory and the capillary endothelium theory. Hauptmann & Gärtner (66) and Hoff (82) clearly formulated the hypothesis that the barrier is located in the perivascular pia-glia membrane. This membrane was thought to be composed of the invaginating pia which follows the vessels from the surface into the depth of the brain, supported by a closely adherent layer of astrocytes (fig. 4). Standard histological techniques and light microscopy failed to reveal whether or not this double membrane accompanied the vasculature throughout its terminal ramifications, enveloping the capillaries. However, in electronmicrographs (figs. 2, 4) of cerebral capillaries, astrocytic feet can be found in association with most of the capillary surface (114). Maynard *et al.* (114) claim that the expanded astrocytic processes form but a single incomplete layer around capillaries and do not overlap one another to any extent. They estimate that this 'sheath' covers about 85 per cent of the total capillary surface and state that the pia does not continue down to surround the capillaries, providing a mesodermal barrier between the vessels and the ectodermal elements of the central nervous system, as had been proposed. At that level, the morphological blood-brain barrier consists only of the

capillary wall itself and the investing sheath of astrocytic end feet.

Tschirgi (146) re-examined the two theories and concluded that the perivascular glial membrane was the more probable site of barrier activity. His arguments were soundly belabored by Bakay (9), Gröntoft (60), Rodriguez-Peralta (127), Maynard *et al.* (114, see above) and no doubt others who have been unintentionally overlooked. Rodriguez-Peralta (127) studied the histologic site of the hematoencephalic barrier with the aminoacridine dye proflavine HCl which stains the nuclei of the cells of all tissues except those of the central nervous system after intravenous administration. The dye does not enter the vascular endothelium of the cerebral blood vessels, in contrast to the endothelial cells of other tissues, and consequently he concludes that the blood-brain barrier is localized in the endothelial cell membrane facing the lumen. Since the dye penetrates the choroidal epithelium but does not enter the cerebrospinal fluid, he proposes that the cell membrane of the choroidal epithelium facing the ventricular lumen constitutes the blood-cerebrospinal fluid barrier. Proflavine does penetrate the superficial pia-glia membrane following subarachnoid administration and also penetrates the intraneural vascular endothelium. Because of this, and the prompt appearance of the due in extraneural tissue following its intrathecal administration, Rodriguez-Peralta suggests that the neural vascular endothelium is permeable from the direction of the central nervous system, and the blood-brain barrier is thus polarized. Intraventricular injection of the dye readily stained the parenchyma adjacent to the ependymal walls, indicating that the ependymal cells do not impose a significant barrier to this substance.

Earlier investigations by Broman (20) using trypan blue are in essential agreement with these results, and there is widespread unanimity of opinion at the present time that the essential barrier to the movement of dyes into the central nervous system from the plasma resides within the capillary endothelium (1, 2, 9, 20, 60, 137).

Maynard *et al.* (114) present the following opinions regarding the blood-brain barrier, based on their electronmicrographs of the vascular bed of rat cerebral cortex such as that here reproduced as figure 2.

"In seeking a locus for the blood-brain barrier, it may be very significant that the endothelial cells of central nervous system capillaries form a completely continuous layer without any suggestion of the fenestrations that have been seen in other capillaries such as are well established in the kidney (123) and have also been observed elsewhere. . . . Quite likely this is a common feature of capillaries in the body generally, and the capillaries of the brain differ significantlyin having an uninterrupted endothelium. . . .

"The present authors believe that the 'blood-brain barrier' may be mainly an illusion. Physiologists have been led to postulate its existence on the assumption that there are considerable extracellular tissue spaces which would be in equilibrium with blood plasma, if a barrier did not exist. We see, however, that the basic assumption is incorrect and that these tissue spaces simply do not exist (135).

"When the physiologist quantitatively studies the penetration of ions, organic crystalloids, proteins, vital dyes, etc. into nervous tissue, he must actually be studying the penetration (or lack of it) into the glial nervous cells. . . . Thus, we believe that the physiological data available should be re-interpreted on the assumption that nearly all substances are within cytoplasmic compartments. Under these circumstances there would be no expectation of a simple correlation with their distribution into the blood plasma. The commonly accepted laws of permeability, which apply elsewhere in the body, may thus indeed apply in the brain without important exception and without invoking a specialized barrier."

Dempsey & Wislocki (30) on the basis of electronmicrographs of rat brains following *in vivo* administration of silver nitrate, have implicated the capillary basement membrane as the probable site of the blood-brain barrier (figs. 2, 4). They observed silver deposits within the endothelium of the capillaries and thought that it could not proceed across the basement membrane. Maynard *et al.* (114) agree that the basement membrane is a continuous structure, but do not believe that it differs from basement membranes found in relation to capillaries elsewhere and are unwilling, therefore, to emphasize its possible role in the blood-brain barrier phenomenon.

Hess (72, 73) has described a homogeneous positive periodic acid-Schiff reaction between the cells, dendrites, axon terminations and neuroglia fibers of the adult central nervous system which he interprets as indicating the presence of a carbohydrate-protein ground substance. This positive periodic acid-Schiff reaction appears in grey matter of the mouse between 5 and 14 days postnatally, and is believed by Hess to determine the presence or absence of the ability of intravenously administered trypan blue to stain the brain and, therefore, the absence or presence of the blood-brain barrier.

The role of the meningeal tissues in the hemato-encephalic barrier has been studied by Rodriguez-Peralta (128), using aminoacridine dyes. Intravenous injections of these compounds result in staining of the dural blood vessels and dural tissue including the mesothelial cells lining the inner dural surface, but they do not penetrate into the arachnoidal tissues or cerebrospinal fluid. This shows, according to this author, that the dural blood vessels share the permeability characteristics of all blood vessels outside the central nervous system, and that there is a dural barrier located in that part of the membrane of the mesothelial lining cells facing the subdural space. Absence of staining of the endothelium of the pial blood vessels indicates that there is a pial barrier, similar to this author's previous description of the blood-brain barrier (see above), located in that part of the membrane of the pial vascular endothelium facing the lumen of the vessel. All of these membranes appear to be one-way barriers, since subarachnoidal injections of aminoacridines stain all the meningeal tissues and the walls of their blood vessels.

In the face of this multiplicity of data and opinion, where is the blood-brain barrier? Unfortunately, radiotracer studies have not provided a direct answer to the question of anatomical locus for the retarded penetration of inorganic ions into the central nervous system, although Bakay (9) has shown with microscopic radioautographs that the walls of the larger arteries of the brain concentrate large amounts of $P^{32}$. This technique unfortunately does not provide sufficient resolution to answer the important question concerning penetration of capillary endothelium.

What is the milieu of the central neurons? Is it an aqueous, protein-free solution of inorganic electrolytes, gases and metabolites? Is it the adjacent membrane of glia cells and fibers? Is it a proteinaceous 'ground substance' of complex structure and obscure chemical reactivity? These questions have, as yet, no final answer.

## DYNAMICS OF THE CHEMICAL MICROENVIRONMENT

### *Electrolyte Exchange*

The exchange of solvent and solutes between the vascular and extravascular compartments of the central nervous system has received renewed attention since the availability of radioactive isotopes has enabled physiologically important substances to be labeled and traced. Among the early studies devoted to this problem, the classic paper of Greenberg *et al.* (58) demonstrated incontrovertibly that the rate of equilibration of a variety of inorganic ions, both negatively and positively charged, with the extravascular fluids of the central nervous system after intravenous administration was uniquely slower than their rate of equilibration with most other tissues. These authors arranged labeled ions in the following order of rapidity of entrance into the cerebrospinal fluid: potassium, sodium, bromide, rubidium, strontium, phosphate, iodide. They interpreted these variations in rate of equilibration as signifying selectivity of the barrier for different solutes.

Early observations of marked and prolonged dehydration of the central nervous system following intravenous hypertonic salt solutions—a reaction not occurring in other tissues—was presumptive evidence that the central nervous system was penetrated only with difficulty by these ions. Schaltenbrand & Bailey (134) perfused hypertonic sodium chloride solution (10 per cent) through one carotid artery of a dog and distilled water at equal pressure through the other. The hydrodynamics of the cerebral circulation are such that the two perfusates remained essentially unmixed, and consequently one half of the brain was perfused with a hypertonic solution and the other half with a hypotonic solution. The animal shortly succumbed, with convulsions limited to the side of the body opposite the hemisphere receiving the hypertonic saline. Gross examination of the brain revealed the side perfused with hypertonic saline to be shrunken and dehydrated, whereas the side receiving the hypotonic solution was swollen and edematous. Microscopic examination of the side receiving the hypertonic saline revealed large, distended perivascular (Virchow-Robin) spaces separating the vessel walls from the glial membrane; and on the parenchymal side of this membrane, the intercellular spaces were described as markedly reduced, and in many areas almost obliterated, so that the cells were packed tightly together. On the side perfused with hypotonic solution there were no perivascular spaces and the intercellular spaces were greatly enlarged. The authors conclude that the perivascular glial membrane is relatively impermeable to sodium chloride. It should be added, parenthetically, that this interpretation also requires the vascular endothelium to be relatively permeable to sodium chloride, thus tending to localize this aspect of the blood-brain barrier in the perivascular glia. Bakay (9) dismisses this study with the statement, "I do not believe that one can come to a definite conclusion from an experiment of such short duration," and describes his own

modification of the experimental procedure in which he was unable to discover any change in $P^{32}$ uptake in the cerebral hemisphere perfused with 50 cc. of 10 per cent saline. He presents this result as if it constituted a refutation of the conclusions of Schaltenbrand & Bailey, but the pertinence of his study seems somewhat obscure.

The panvascular nature of this phenomenon was further emphasized by the demonstration that the predominantly extracellular ion, chloride, required 48 min. to replace one third of the brain chloride after intravenous administration in rabbits, whereas virtual equilibrium with the plasma chloride was reached within 11 min. for the majority of tissues (111). Hahn & Hevesy (63) demonstrated that only 3 per cent of the central nervous system sodium exchanged after 11 min., 12 per cent after 2 hr., and equilibrium was not reached for 62 hr. following parenteral administration of $Na^{24}$.

Experiments with radioactive potassium indicated that this primarily intracellular ion exchanges between plasma and central nervous system somewhat more rapidly than sodium, but still many times more slowly than in extraneural tissues (118). Katzman & Leiderman (89) used $K^{42}$ to determine the influx and outflux of brain potassium in rats. They found the influx to be 2.89 mEq per kg per hr., the outflux rate 3.64 mEq per kg per hr., and the influx-outflux ratio 0.80. Since a steady state obtains, the outflux must be equivalent to influx, and therefore these authors conclude that 20 mEq K per kg wet brain is not exchangeable with parenterally administered $K^{42}$. They speculate that this nonexchangeable potassium may reside within a pool behind an impermeable membrane either at the capillary, cellular or intracellular level, or may represent chemically bound potassium, as suggested by Folch (43) who established that there is an excess of cations over common anions in the brain amounting to 26 mEq and showed that this anion deficit is accounted for by complex lipids capable of binding potassium.

Katzman & Leiderman found that the potassium influx-outflux ratios changed markedly with development. Up to 35 days of age, rats showed no binding of potassium. Adrenalectomy did not appreciably change the influx in adult animals, but caused an increase in influx-outflux ratio, indicating that all brain potassium became exchangeable. Cortisone in adrenalectomized animals restored the nonexchangeable compartment whereas deoxycorticosterone and saline had no effect.

Despite varying plasma potassium levels the potassium influx into the brain remained approximately the same, leading to the suggestion that the inflow of potassium in adult animals may be a carrier-limited one. These results are similar to the behavior of glucose in the isolated perfused cat brain (see below), which also appears to be transported into the central nervous system by a reaction which becomes carrier-limited at high blood-glucose concentrations.

Following intravenous administration of labeled tracer doses, bromide, iodide, thiocyanate, phosphate and chloride equilibrate throughout the body's extracellular water within a few minutes, except in the central nervous system where they are not even approximately in equilibrium after 3 hours.

### *Potassium to Calcium Ion Ratio and Brain Function*

Many workers have investigated the relationship between the ionic composition of the fluid environment of the central nervous system and various aspects of central nervous system function. The majority of these studies have been conducted on anesthetized animals, in which the relationship between central ionic concentration and *a*) various autonomic functions or *b*) the electrical activity of the brain was observed.

Two methods of altering central ionic concentrations have been employed: intracarotid injection of solutions of varying ionic composition; and direct central introduction of such solutions either by injection into the cisterna magna or the lateral ventricles, or by perfusion of the ventricular system of the brain with an artificial cerebrospinal fluid appropriately modified. Some differences exist between the results observed with these procedures and are to be attributed to differences in the distribution of materials presented via these different routes. In general, however, the results are in agreement. It is clear that the ionic composition of the cerebrospinal fluid plays an important role in the maintenance and variation of membrane potentials in the central nervous system, and in the function of central mechanisms involved in behavior and in the regulation of autonomic processes.

In 1899 Meltzer (115) described the effects of intracerebral injections of potassium chlorate in rabbits in an effort to ascribe the toxicology of this substance to its action on the central nervous system. He observed that: "The injection of 3 minims of a 5% solution of $KClO_3$ into the brain of rabbits causes at once a long series of convulsions, forced movements, opisthotonus, coordinated movements, incoordinated clonic and tonic convulsions, etc. This state of excita-

tion gradually gives way to a comatose state which not many animals survive. Stronger solutions cause a more stormy scene, but of shorter duration; the animal succumbs in 15 to 20 minutes. When 3 minims of a 1% solution are injected the animal runs about incessantly for an hour and longer and then falls into a paretic state lasting for hours; but the animal recovers."

Meltzer also demonstrated the opposite effect of intracerebral injection of magnesium sulfate, following which the rabbit became paralyzed in a short time without preceding convulsions.

The studies of Stern & Chvoles (140), Resnik *et al.* (125), Mullins *et al.* (117), Stern (138, 139), Downman & Mackenzie (31), von Euler (154), Walker (156), Leusen (100, 101), Koenigstern (96), and Horsten & Klopper (83) provide a full survey of the effects of intracisternal and intraventricular injections of $K^+$ salts and of modifications in the electrolyte balance produced in other ways in the cerebrospinal fluid in the region of the medulla oblongata. In general, when a solution with an abnormally high $K^+$–$Ca^{++}$ ratio (due either to excess $K^+$ or deficient $Ca^{++}$) is injected intracisternally, there is initially increased muscular activity and stimulation of respiration, followed by a rise of arterial pressure and cardiac slowing. Small doses of KCl usually produce an initial fall of arterial pressure (from 50 to 120 mm Hg) associated with bradycardia. With sufficiently large doses of KCl, respiratory stimulation is replaced by apneusis, associated with circulatory collapse. These effects are generally attributed to an action, first stimulant and then depressant, on the various medullary centers, vasoconstrictor, vasodilator, cardioinhibitory, cardioaccelerator, respiratory, etc.

Stern & Chvoles (140) found that the introduction of potassium into the cerebral ventricles of dogs and cats caused an elevation of the arterial pressure, and a stimulation of the pressor and an inhibition of the depressor reaction of the carotid sinus reflexes. They noted, on the other hand, that calcium had a reverse effect, and that injection of equivalent amounts of $Ca^{++}$ and $K^+$ had no effect. They concluded that the $Ca^{++}$–$K^+$ ratio is the significant quantity in determining central nervous system excitability. von Euler (154) also obtained an elevation of arterial pressure in the cat following intracisternal injection of KCl and reported that calcium had little effect, although it neutralized the action of potassium. Similar results had been reported by Resnik *et al.* (125) following intracisternal administration of KCl in dogs, with the exception that very slight concentrations of potassium lowered the arterial pressure. Walker *et al.* (156) concluded that potassium produces a general stimulation of the central nervous system, contrary to Stern & Chvoles (140) who believed that the sympathetic centers are stimulated while the parasympathetic are depressed.

Leusen (100) agrees with the interpretation of Walker *et al.*, on the basis of his studies with perfusion of the cerebral ventricles in dogs after vagotomy and carotid sinus isolation. He found that an excess of potassium in the perfusate of the cerebral ventricles raised the arterial pressure and enhanced the vasomotor reflexes whereas perfusion of the cerebral ventricles with a potassium-free solution had no effect on these indices. An excess of calcium or magnesium in the perfusate caused a depression of the arterial pressure and of the vasomotor reflexes.

Sabbatini in 1901 (131) clearly demonstrated the importance of the calcium ion concentration on the activity of the cells of the central nervous system. By comparing the gross effects produced by lowering the calcium of the blood serum (64) with those produced by the injection of sodium citrate into the cisterna (84), it could be inferred that the calcium ion concentration in the cerebrospinal fluid is of far greater importance for the production of peripheral neuromuscular symptoms than is the calcium ion concentrations of the blood serum.

In this regard, Rubin *et al.* (130) recorded the cortical electrogram and the simultaneous electrocardiogram of cats during the intravenous injection of salts of potassium, calcium and magnesium. Potassium and calcium produced no changes in the cortical electrogram until the development of intraventricular block or of cardiac arrest, at which time slowing of the cortical electrogram developed. Magnesium, however, produced transient periods of slowing before pathological changes appeared in the electrocardiogram. This immunity of the central nervous system to drastic changes in blood concentrations of $K^+$ and $Ca^{++}$, compared with its sensitivity to alterations in cerebrospinal fluid concentrations of these cations, is a further dramatic illustration of the homeostatic regulatory mechanism resident in the blood-brain barrier.

When the calcium concentration of the cerebrospinal fluid was lowered, either by repeated withdrawal of cisternal fluid and its replacement with calcium free cerebrospinal fluid or by intracisternal injection of sodium citrate, there resulted a marked increase in muscular activity which could be easily detected before any marked change in arterial pres-

sure or respiration was observed. If the calcium concentration was reduced sufficiently a severe state of tetany supervened (117). "The animal (dog) showed marked opisthotonus, pleurothotonus, and dorsal curvature of the tail, as well as extensor rigidity of the legs and contracted abdominal musculature. The neck and foreleg phenomena came on first. Accompanying these symptoms, there was an elevation of blood pressure with a slowed heart. (After curare these circulatory effects were much less marked and the pronounced neuromuscular changes were abolished.) Respiration was markedly increased, and during severe attacks it became very dyspneic."

Increased central calcium ion has been demonstrated to have the opposite effect from potassium ion, to directly oppose the action of raised central potassium concentration, or to do both, on all of the autonomic functions described previously.

The effect of increased central potassium ion on the higher frequency electrical activity of the brain appears to be biphasic. Small increases in potassium ion raise the frequency and decrease the amplitude of the EEG (17, 22, 32, 69, 100, 126), indicating a modification of cortical excitability. Larger increases in potassium ion decrease the frequency and increase the amplitude of the EEG (17, 32). Investigations of both evoked and spontaneous potentials show a differential susceptibility of these to changes in potassium concentration. Small intracarotid injections of potassium chloride have no effect on the primary response of the auditory cortex to clicks but intensify the after-discharge. Higher intracarotid doses of potassium ion will block the after-discharge. Auditory cortical responses to a continuous sound are reinforced with low potassium chloride doses and decreased with higher doses.

Increased central calcium ion decreases the frequency and increases the amplitude of the EEG (17, 32, 69, 126), indicating a decrease in cortical excitability comparable to that achieved by large increases in central potassium. Work on both evoked and spontaneous potentials indicates that raised calcium ion concentration has no effect on the primary evoked cortical response but blocks the after-discharge. Heppenstall & Greville (69) conclude that neither potassium nor calcium ions can influence sensory transmission to the cortex, but neurons which respond to the arrival of afferent impulses at the cortex, probably internuncial neurons in upper cortical layers, can be excited or depressed by these ions. Horsten & Klopper (83), however, believe that the cortical effects of ion shifts are not achieved via direct cortical action but rather via effects of these ions on the reticular formation. They argue that all effects of altered cerebrospinal fluid ionic composition on brain electrical responses which are reported in the literature can be viewed as consequences of ionic action on brain-stem centers, and that the observed cortical waves arise from synchronous fluctuations in membrane potentials governed by subcortical structures.

As with the autonomic effects of imposed central ionic shifts, the effects of altered central potassium on EEG can be opposed by calcium (17, 32, 69, 104, 126). These authors agree that the inhibitory action of calcium ion occurs more slowly than the blocking produced by large potassium ion increases.

The evidence points to the importance of the potassium-calcium ratio, rather than either ion per se, in these modifications of electrical activity. Gerard (53) points out that potassium ion and calcium ion, both inhibitory in high concentrations, nevertheless cancel each other's effects on the EEG, which can be interpreted as an indication that two independent and antagonistic mechanisms exist for the suppression of cortical electrical activity.

The effects of altered central nervous system ionic concentrations on the gross behavior of the intact unanesthetized animal have not been extensively investigated. The occurrence of seizures after administration of intracisternal (96), intracerebral (115) or hypothalamic (24, 29) potassium has been reported. Koenigstern described scratching attacks in cats after intracisternal potassium ion, which were reversible with calcium ion administered via the same route (96). Calcium injected into the cisterna magna (96), the lateral ventricles (40), or the infundibular region (24, 29) has been reported to cause sleep or unconsciousness. One worker (96) reports convulsive episodes on some occasions after calcium injections into the cisterna magna. John and co-workers (86) studied the effects of intraventricular injections of cations on conditioned responses in unanesthetized cats trained to avoid shock on the presentation of visual or auditory stimuli or both, and to discriminate visual patterns for food. Both calcium and potassium markedly interfered with the performance of learned tasks, and in similar ways. Furthermore, calcium did not counteract the effect of potassium in this regard, leading these authors to conclude that the crucial factor sensitive to central potassium and calcium injections is not the threshold of a neuron to an impinging stimulus, but the phasing of signals to arrive at some integrating structure in proper time relationship.

*Water Exchange*

The question of water exchange between plasma and brain has been investigated by Bering (13) and Sweet *et al.* (145) who have shown that intravenously injected deuterium-labeled water rapidly enters all areas of the brain and the cerebrospinal fluid, reaching equilibrium with the blood in about 20 min. The time required for the cerebrospinal fluid concentration of deuterium to achieve one half its concentration in the blood was 1.5 min. for the cisterna magna, 8 to 11 min. for the ventricles, and 18 to 26 min. for the lumbar sac. Equilibrium with the grey matter of the cortex occurred within 1 min. Blockage of the cerebrospinal fluid system did not alter the rate of deuterium diffusion, and it can be concluded that water exchanges among the vascular and extravascular compartments of the central nervous system more rapidly than in most tissues, as a result, most probably, of the relatively dense vascularization of the central nervous system. This free passage of water requires that the intracranial fluids be essentially isotonic at all times.

*Exchange of Metabolic Intermediates*

With respect to organic crystalloids, the blood-brain barrier has been invoked to explain awkward discrepancies between *in vivo* and *in vitro* results of metabolic substrate utilization. Although in the *in vivo* situation, only glucose, and to a lesser extent glutamic acid, mannose and maltose plus a few other substrates have been found capable of restoring normal electroencephalographic patterns or consciousness following insulin shock or hepatectomy hypoglycemia (108, 113), brain brei or slices not only can oxidize the above compounds, but also lactate, $\alpha$-ketoglutarate, succinate, fumarate, pyruvate and other intermediates (36, 106, 162). The rate of transfer of fructose, lactate, glutamate and succinate from blood to brain is much slower than that of glucose, and may be insufficient to support adequate functional metabolism (93, 94). However, it must not be assumed that the ineffectiveness of substrates *in vivo* to support central nervous system function is a priori evidence that they do not penetrate the blood-brain barrier. It is possible that substances both penetrate and are metabolized, but are somehow not geared to the metabolic machinery necessary for normal function. In this respect, pyruvate does appear to penetrate into brain tissue rapidly where it is converted to lactate, but it has been proposed that the rate of formation of this latter compound is insufficient to provide adequate metabolic energy to the central nervous system (36). Likewise, succinate *in vitro* causes a marked increase in oxygen uptake of brain breis and slices, but little or no increase in carbon dioxide production. It is oxidized rapidly through only one step, to fumarate and malate, and further oxidation takes place very slowly (37). Thus, even if succinate penetrated readily into the central nervous tissue from the blood, it is quite unlikely that it could support function effectively.

Glutamic acid and glutamine together comprise approximately 50 per cent of the $\alpha$-amino nitrogen of the nonprotein fraction of the brain, and glutamic acid is the only amino acid which has been found to be oxidizable by this tissue (162). Following intravenous administration of large amounts of glutamic acid, there was no increase in brain concentration of this substance. However, after intravenous injection of glutamine, singificantly higher brain concentrations of glutamic acid were found in a number of experiments (155). From these studies, Waelsch concluded that the blood-brain barrier is normally permeable to glutamine, and this substance may therefore furnish the amino group for amino acids such as alanine, aspartic acid and glutamic acid the carbon structure of which is generated through the citric acid cycle in the central nervous system. Himwich *et al.* (79) suggest that the impermeability of the blood-brain barrier to glutamic acid is a function of age. They found that free glutamic acid enters the brain easily in rats 24 hr. old but does not penetrate readily at older ages.

*Glucose Exchange*

The clinical use of intravenous hypertonic glucose solutions to produce cerebral dehydration presents direct evidence that the entry of glucose into the central nervous system is a more complex process than its entry into most tissues. Although the dehydration so produced is short-lived and supplanted by movement of water into the brain as the glucose is taken up by that organ, nevertheless no delay of this sort occurs in the movement of glucose into the interstitial space of other tissues. Geiger and others have investigated this blood-brain glucose transport by means of an *in situ* brain perfusion technique in which the arterial supply and venous drainage of the cat brain are isolated from the general circulation and perfused, via an external circuit, with a 'simplified blood' consisting of washed beef erythrocytes suspended in Krebs'-Ringer's solution, containing 7 per cent native bovine serum albumin (49). With this

preparation it has been possible to maintain brain functions (normal corneal reflex, pupillary reactions to light, natural respiration, maintenance of systemic arterial pressure and vasomotor responses, normal electrocorticogram, spontaneous blinking and movements of facial structures, and easily elicited cortical electrical responses to stimulation of an extremity) for over 4 hr., under appropriate circumstances.

The glucose content of the brain was normally found to be 25 to 40 per cent lower than that of the blood, and small variations in blood glucose concentration were followed by proportionate changes in the brain, as had been reported previously (62, 90, 119). However, if the blood glucose concentration was elevated considerably beyond the normal ranges of variations, then the brain glucose concentration did not increase proportionately. For example, increasing blood glucose concentration to 800 mg per cent increased the brain glucose content to only 300 mg per cent, and subsequent increase in blood glucose to 1600 mg per cent produced only negligible further increases in the brain. Such an effect is compatible with the concept of a metabolic pump transporting glucose from the plasma into the central nervous system. The finite capacity of such a pump could become limiting at sufficiently high blood glucose concentrations, and further increases in the glucose 'reservoir' would not increase the maximum rate of transport across the blood-brain barrier.

Further evidence for such an active glucose transport system resulted from the observation that unless a freshly isolated liver was included in the perfusion circuit, the brain could be maintained for only brief periods. Without the liver (or liver extract), the glucose content of the cerebral cortex progressively diminished in spite of high glucose concentrations in the blood. This impairment of glucose uptake by the brain in the absence of liver could be prevented by the addition of two nucleosides, uridine and cytidine, to the perfusion blood (51). If glucosamine was added to the perfusion blood at a time when glucose uptake was blocked, this amine was taken up and phosphorylated by the brain.

In the blood-brain barrier glucose transport process, it is possible that the sugar is chemically altered in such a way that it becomes 'acceptable' to the functional cells of the central nervous system. The results of Wolff & Tschirgi (165) may indicate that the central nervous system utilizes glucose only if this is taken up from the plasma, across the blood-brain barrier, and not if introduced via the cerebrospinal fluid. In these experiments, the blood-sugar level of anesthetized cats was reduced by insulin until the disappearance of the patellar reflex. Subsequent perfusion of the spinal subarachnoid space for hours with Ringer's solution containing 100 to 600 mg per cent of glucose, between a lumbar and cisternal tap, failed to restore the reflexes, which were, however, readily restored by intravenous glucose injections. Alteration of $Ca^{++}$ or $K^{+}$ concentration in the perfusate produced immediate changes in spinal reflexes, respiration and pupillary size, indicating the availablility of the perfusate to neural elements.

On the other hand, the ineffectiveness of intrathecal glucose for maintaining normal spinal cord function may be simply due to the diffusion distance from the subarachnoid space to the central grey substance. If, as discussed above, no centripetal flow of cerebrospinal fluid occurs into the depths of the spinal cord substance, then it seems quite likely that the rate of delivery of glucose from the spinal subarachnoid space to the neuron perikarya would be insufficient to support normal metabolism. Subarachnoid alterations of $Ca^{++}$ or $K^{+}$ could readily produce changes in motor activity by influencing the superficial fiber tracts or grey matter immediately adjacent to the subarachnoid space.

Extensive investigations with cell types other than nervous tissue have shown that glucose transport into other living cells does not follow the laws of simple diffusion but apparently involves some active chemical process. Phosphorylation was thought to be part of the transport mechanism in the intestinal absorption of sugars (68, 107, 152), but recent studies have shown that the process is more complex, apparently involving alteration of the glucose carbon skeleton itself (74, 75). Considering the effect of cytidine and uridine on sugar uptake and oxidation by the brain, Geiger (49) proposes that the polysaccharide synthesis via glucuronic acid and glucosamine may be involved in the blood-brain glucose transport mechanism. This hypothesis is based on the observation that in penicillin-treated staphylococcus aureus, a compound formed by the coupling of uridine, glucosamine and amino acids is accumulating at a high rate (121, 142). This compound is postulated to be the precursor of the cell wall, inhibited from further conjugation by the presence of penicillin. As mentioned previously, glucosamine is taken up and phosphorylated by the perfused cat brain when glucose is unable to penetrate the blood-brain barrier, and the existence of glucosamine-containing mucopolysaccharides in nerves and brain has been recently demonstrated (54). Insulin, postulated to influence importantly the

rate of glucose transport across cell membranes generally (102), does not penetrate into the brain from the blood (67); but when added to the perfusion fluid in perfusion experiments, it slightly increased the rate of sugar oxidation by the brain (4).

*Glucose and Brain Function*

The dependence of the brain on a minute-to-minute supply of glucose from the blood for maintenance of function and electrical activity has become an axiom of neurophysiology (see the preceding chapter in this volume by Sokoloff). The use of insulin hypoglycemia in schizophrenia (133) has provided dramatic evidence for this relationship in humans. Following a shock dose of insulin there develops a series of clinical changes first described by von Angyal (153) and Frostig (48). The signs and symptoms seem to show progressive allocations down the neuraxis, starting with the cerebral cortex and proceeding towards the medulla oblongata, as shown in the following:

The Five Phyletic 'Layers' (77)

1. Depression of cerebral hemispheres and cerebellum
2. Release of subcorticodiencephalon
   a. Subcortical motor nuclei
   b. Thalamus
   c. Hypothalamus
3. Release of midbrain
4. Release of upper medulla
5. Release of lower medulla

Himwich (77) describes the course of events as follows:

"The first constellation of signs indicates a depression of cortical functions, for example, disturbances of vision and audition occur as the patient, drooling saliva, becomes drowsy and relaxed, and finally loses contact with his environment. Just before loss of environmental contact some patients exhibit a period of wild excitement. Once contact is lost the second stage begins as an entirely new clinical picture is exhibited. In addition to motor restlessness there are primitive movements of many kinds, grimacing, sticking out the tongue, and kissing, as well as forced gasping. At this time sensory stimuli usually evoke exaggerated responses. Release of the autonomic with sympathetic predominant over parasympathetic is marked and comes on in waves as indicated by increases in blood pressure and heart rate, flushing of face, dilatation of pupils, and periodic exophthalmus. It is significant that when convulsions do occur they appear most frequently when the second phyletic layer is released from cortical control. First fine myoclonic twitchings of the facial muscles are observed and then the eyes may deviate to one side. If the larger muscles are seized by contractions which become generalized the patient undergoes grand mal-like convulsions. But in most instances these convulsive episodes do not appear and the patient gradually loses these signs and sinks to the third or mesencephalic phase. This complex tells of the release of midbrain functions reminiscent of the changes observed with high decerebration, namely, tonic spasms with flexion of the arms and extension of the legs. Sometimes the patient twists himself on his long axis in torsion spasms. With each paroxysm blood pressure and heart rate increase . . .. Next signs of low decerebration referable to upper medulla are visible. The legs are still extended, but now the arms are brought back over the head, thus in a remarkable way resembling the decerebrate rigidity produced by surgical operative intervention in lower mammals. Finally the fifth stage appears when the medullary centers are affected by the hypoglycemia. The patient is pallid, the heart rate is slow, respiration is shallow and retarded in rate, pupils are constricted and heat loss is increased."

Administration of carbohydrate causes the patient to retrace his symptomatic progression in the reverse direction. Further support for the conclusion of successive syndromes was provided by Hoagland *et al.* (80) who demonstrated that cortical electrical responses in dogs failed earlier than hypothalamic during progressive hypoglycemia. However, the consensus of most observers is that, except for the initial drop in blood sugar until the patient loses contact with his environment, there is little correlation between the symptoms of hypoglycemia and the amount of glucose in the blood.

These observations have been interpreted as indicating the necessity for maintaining some minimum concentration of glucose in the neuronal milieu, since it has been repeatedly demonstrated that the only energy-yielding substance taken up from the blood by the brain, in amounts large enough to satisfy its energy requirements, is glucose (76). However, during perfusion experiments of the suprasylvian gyrus of the cat using glucose-free oxygenated Ringer-albumin solution, it was observed that the perfused cortex maintained its excitability and its oxygen consumption for up to 2 hr. (59). Equally surprising are the results of Geiger *et al.* (50) who report that the isolated perfused cat brain can be maintained with normal electroencephalograms and reflex activity for $1\frac{1}{2}$ hr. using a glucose-free perfusate, provided that

the rate of perfusion is increased to three times normal. Under these conditions, no metabolic substrate whatsoever is available from the vascular compartment, and the intrinsic glucose of the brain is exhausted within 15 min. Since the amount of endogenous glycogen does not diminish during this period, and since the respiratory quotient decreases from its normal value of approximately 1.00 to between 0.84 and 0.56, it is apparent that noncarbohydrate 'structural' components of the central nervous system are being catabolized. Studies with $C^{14}$ labeled glucose (49) have shown that only 30 to 35 per cent of the glucose taken up by the brain is directly oxidized to carbon dioxide and water under 'resting' conditions, and an even smaller percentage during activity. Another 20 to 30 per cent of the glucose taken up is rapidly transformed into acid-soluble components (largely amino acids), and substantial amounts are built into lipids, proteins and other acid insoluble components. Further studies confirmed the fact that proteins, lipids and other nonsoluble substances are being constantly metabolized by the brain. Therefore, it is proposed by Geiger that the ability to maintain a functional central nervous system in the absence of blood sugar is dependent upon the maintenance of a blood flow rate rapid enough to eliminate waste products originating from the noncarbohydrate metabolism. (Further comments on Geiger's studies will be found in the preceding chapter in this volume.) A similar interpretation was proposed by Gellhorn & Kessler (52) to explain their observation that under certain conditions in rats it is possible for the electrical activity of the cortex to be normal with the blood sugar at coma level. They first removed the adrenal medulla bilaterally in adult male rats. One or more weeks later when coma had been produced by insulin injection, the brain was subjected to an electric shock. This was followed immediately by disappearance of the coma, by normal behavior and by return of the EEG to the original pattern although the blood sugar was still at coma level. These effects were explained as resulting from the increased blood supply to the brain through excitation of the sympathetic nervous system. These observations suggest the possibility that the blood-brain barrier may be as importantly a process of eliminating substances from the neuronal milieu as in regulating solute entry from the plasma.

### *Oxygen Exchange and Brain Function*

There is no evidence to indicate that a barrier to oxygen exchange exists between the blood and the central nervous system extravascular fluids, and neural function rapidly deteriorates following oxygen deprivation. In general, the symptomatic progression due to hypoglycemia (see above) is duplicated in acute anoxia, except that in the latter case the events are compressed into a few minutes instead of hours. Sugar & Gerard (143) produced sudden and complete cerebral anemia in cats by temporary occlusion of all vascular channels to the brain, and observed that the electrical activity of the cortex and caudate nucleus disappeared earlier than that of the thalamus and medulla. Provided that the anemia was not maintained to the point of irreversible damage, recovery occurred in the reverse order. The survival times of the electrical activity in various cerebral structures, following acute anemia, as found by Sugar & Gerard (143) were as follows:

| | |
|---|---|
| Cerebral cortex | 14–15 sec. |
| Caudate nucleus | 25–27 sec. |
| Ventrolateral thalamic nucleus | 28–33 sec. |
| Medullary reticular formation | 30–40 sec. |

The ability of the central nervous system to continue to function in the absence of oxygen decreases with age in many species and irrespective of the manner of producing anoxia (76, chap. 7). Newborn rats are able to survive at 320 mm Hg atmospheric pressure four times as long as adults. The tolerance declines rapidly after birth until the third week when the mature level is first attained. There is an associated shift from anaerobic towards aerobic supply of cerebral energy, so that the difference between the central nervous system caloric requirement and the anaerobic supply becomes greater in the adult.

### *Transbarrier Potential Difference and Hydrogen Ion Exchange*

The role of electric charge in the homeostasis of the neuronal milieu has received considerable attention since the early observation that acidic dyes behaved differently from basic dyes in staining the brain *in vivo*. The significance of solute charge was intensively explored and discussed by Friedmann (44) using aniline dyes, toxins, viruses and drugs, and Becker & Aird (11) emphasized the possibility that a charged membrane might be involved in explaining the effect of acidic dissociation constant on the permeation of certain sulfonamides into the brain (56).

Tschirgi & Taylor (150) described an electrical

potential difference between the blood stream and the intracranial extravascular fluids which was uniquely sensitive to $[H^+]$ and $[K^+]$, obeying the following relationship with respect to pH:

$$\Delta P.D._{mv} = k\Delta \log_{10} \frac{[H^+]_a}{[H^+]_i}$$

where $[H^+]_a$ is the hydrogen ion concentration of the arterial blood and $[H^+]_i$ is the hydrogen ion concentration of the central nervous system interstitial fluid. For the central nervous system-blood potential difference in millivolts between cerebral cortex and jugular blood of rabbits and rats, $k$ was found to be $29 \pm 5$ mv. These results are interpreted as indicating a source of emf across the panvascular blood-brain barrier which resembles a membrane diffusion potential. The blood-brain barrier is postulated to be more permeable to $H^+$ and $K^+$ than to anions and other cations, and the presence of this electrical potential is proposed to be related to a secretory process involved in regulating the central nervous system environment.

This electrical evidence for relatively free movement of $H^+$ across a membrane separating the plasma from the central nervous system extravascular fluids does not require that changes in plasma $[H^+]$ are readily reflected in extravascular fluid $[H^+]$. On the contrary, analogous to nerve cell membranes where $K^+$ permeability is relatively high, but little net movement of this ion occurs, it is suggested that although the mobility of $H^+$ across the blood-brain barrier is high, net movement of this ion between the intravascular and extravascular compartments is limited by electrostatic forces because of the sharply reduced mobilities of $Cl^-$ and other anions. The relative inability of metabolic acidosis and alkalosis to produce a change in cerebrospinal fluid pH has been described by De Bersaques (28) following intravenous infusion of HCl or $NaHCO_3$ solutions. Leusen (99, 101) had previously discussed the rapid and marked changes in cerebrospinal fluid pH which accompany respiratory acidosis and alkalosis produced by inhalation of gases with high $CO_2$ contents, or hyperventilation. As early as 1925, Cestan *et al.* (21) measured pH of the blood and cerebrospinal fluid during acidosis induced by morphine and chloroform anesthesia, and reported that under these circumstances the changes in $H^+$ concentration of these two fluids paralleled each other. They noted further that experimental acidosis produced by intravenous injection of HCl did not decrease the pH of the cerebrospinal fluid, but instead caused it to become slightly more alkaline. It has also been shown that the movement of $HCO_3^-$ from plasma to cerebrospinal fluid must occur at an exceedingly slow rate in view of the slight change in cerebrospinal fluid alkali reserve following intravenous administration of $NaHCO_3$ in amounts sufficient to markedly increase the alkali reserve of the plasma (25). Therefore it appears that the decrease in central nervous system pH during $CO_2$ administration results from the rapid diffusion of molecular $CO_2$ into the extravascular fluids rather than net movement of $H^+$ as such from the plasma.

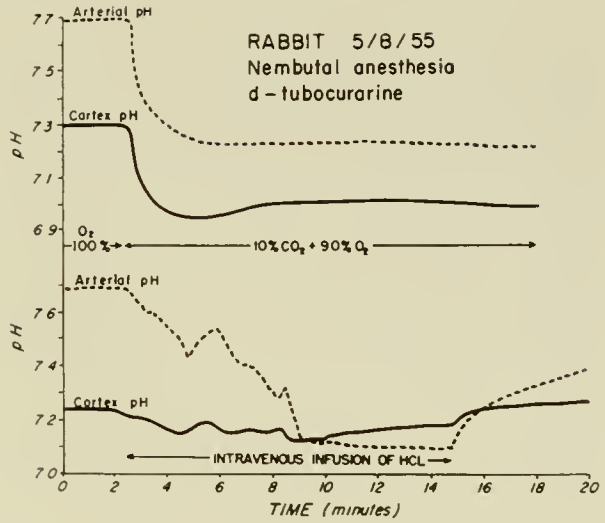



FIG. 7. Representative curves contrasting the lack of effect on the brain pH of intravenous HCl with the depression of brain pH resulting from $CO_2$ inhalation. The initial blood alkalosis was produced by artificial hyperventilation. [From Tschirgi (147).]

These relationships are illustrated in figure 7 (163, p. 136) from data obtained by simultaneous continuous measurement of arterial blood pH and the pH of the surface of the cerebral cortex. During respiratory acidosis (increased $CO_2$), both the hydrogen ion concentration in the blood plasma and in the extravascular interstitial and cerebrospinal fluids increase considerably, with the change in the plasma being somewhat greater. However, for a comparable increase in plasma $[H^+]$ during metabolic acidosis (HCl infusion), little if any change in interstitial and cerebrospinal fluid $[H^+]$ occurs.

To the extent that this barrier to net transfer of $H^+$ from plasma to extravascular fluids is coextensive with the central nervous system vasculature, then to this extent must the functional consequences of directly altering plasma pH not result from an altered

pH of the interstitial fluid. The neuronal environment seems rather secure against $H^+$ concentration changes in the plasma. On the other hand, changes in plasma $CO_2$ are rapidly reflected in a changed interstitial pH as this readily diffusible lipoid soluble gas passes into the extravascular fluid and becomes hydrated. It is interesting to speculate whether this lack of local control by the central nervous system over $CO_2$ movement may not represent an 'Achilles heel' of the blood-brain homeostatic mechanism, necessitating precise regulation of blood $pCO_2$ by the respiratory center to prevent disastrous shifts in pH of the neuronal milieu. In this regard, Swanson *et al.* (144) studied the effect on the EEG of differential regulation of $CO_2$ and pH, and demonstrated in unanesthetized curarized cats that increased arterial $pCO_2$ with lowered blood pH produced EEG slowing progressing to rolling 3 per sec. activity with intermittent flattening. Hypoventilation produced progressively higher amplitudes and 5 to 6 cps activity with a typical sharp configuration. Lowering blood pH without appreciably changing arterial $pCO_2$ by intravenous HCl infusions produced no significant EEG alteration. Intravenous $Na_2CO_3$ and $NaHCO_3$ both raised arterial pH, but $Na_2CO_3$ lowered arterial $pCO_2$ producing hyperventilation-like EEG abnormalities, while $NaHCO_3$ raised the $pCO_2$ producing EEG changes similar to those of $CO_2$ breathing.

Furthermore, it is possible for the pH of the cerebral cortex to vary independently of the blood, as shown by Dusser de Barenne *et al.* (33). They found that in dogs the pH of the cortex passively followed that of the arterial blood when the $CO_2$ content of the latter was varying due to alterations in the ventilation, but that as soon as changes occurred in the functional activity of the cortex, its pH altered independently of that of the arterial blood. Similarly Tschirgi *et al.* (149) demonstrated local changes in cerebral cortex pH of as much as 0.5 units lasting 2–4 min. which accompanied waves of cortical spreading depression or convulsions in cats and rabbits.

### *Transbarrier Metabolic Pump*

As indicated in figure 4, there appears to be a continuous net movement of water and solutes from the vascular compartment into the extravascular compartments of the central nervous system which is balanced, at least in part, by a net movement of water and solutes from the subarachnoid space through the arachnoid villi back into the blood stream (see Davson's chapter on intracranial fluids in this volume). As discussed previously, the thermodynamic analysis of this fluid formation requires local metabolic energy to account for the electrolyte composition of the cerebrospinal fluid (fig. 3), but the nature of this metabolic 'pump' and its role in regulating the neuronal milieu have remained obscure.

Tschirgi and co-workers (148) reported that the carbonic anhydrase inhibitor acetazoleamide (2 - acetylamino - 1,3,4 - thiadiazole - 5 - sulfonamide) given intravenously to cats and rabbits produced a threefold reduction in rate of cerebrospinal fluid flow in an open drainage system, or a decline of approximately 30 per cent in intracranial pressure in a closed system. Subsequent studies (148; unpublished observations) revealed that this effect was unrelated to altered blood $CO_2$ tension, blood pH, altered renal excretion or circulatory hemodynamics, and it therefore was interpreted as resulting from inhibition of the intrinsic carbonic anhydrase of the central nervous system. This effect of acetazoleamide has been confirmed in cats by Kister (92) who also showed that two compounds having close structural and chemical relations to acetazoleamide, but without activity against carbonic anhydrase, were ineffective in reducing flow rate of cerebrospinal fluid. Knapp *et al.* (95) demonstrated a similar reduction in cerebrospinal fluid pressure following acetazoleamide in the cat, but were unable to measure a significant decrease in normal monkeys, due perhaps to the extremely low pressure (15 mm $H_2O$) which they observed in their animals prior to administration of the drug. In both cats and monkeys, these authors recorded an initial transient increase in cerebrospinal fluid pressure which they attribute to increased plasma carbon dioxide and consequent intracranial vascular dilatation. Coppen & Russell (26) reported an initial pressure increase in epileptic patients given acetazoleamide, but did not observe a subsequent fall below preinjection control levels during their 2-hr period of observation.

Carbonic anhydrase occurs in a variety of secretory tissues, including stomach, pancreas, kidney and ciliary body of the eye (27), and is known to be present in appreciable amounts throughout the central nervous system (7). Acetazoleamide has been reported specifically to inhibit this enzyme, which catalyses the reaction $CO_2 + H_2O \rightleftarrows H_2CO_3$ (116), and to alter secretory activity in those tissues where carbonic anhydrase occurs and which are known to possess a secretory function (85).

On the basis of these observations, Tschirgi (147) has postulated a mechanism diagrammed in figure 8, whereby $Na^+$ and $Cl^-$ could be transported from the plasma into the extravascular fluids of the central

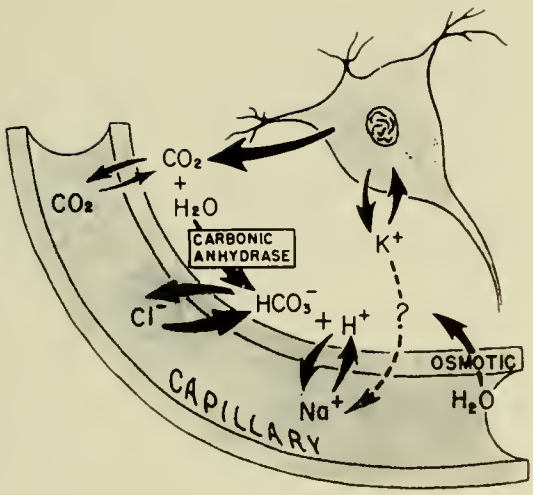



FIG. 8. Diagram illustrating proposed mechanism for converting central nervous system metabolically produced $CO_2$ into carbonic acid with subsequent exchange for plasma $Na^+$ and $Cl^-$. [From Tschirgi (147).]

nervous system by an exchange mechanism operating via metabolically produced $CO_2$ (147, fig. 40). It is proposed that a fraction of the $CO_2$ produced by central nervous cellular metabolism does not diffuse into the blood as molecular $CO_2$ but is rapidly hydrated to carbonic acid in the presence of carbonic anhydrase. This reaction could most reasonably occur within a cellular structure immediately adjacent to the capillary wall separating the blood from the extravascular compartments and, for this reason, is proposed to exist within the neuroglial perivascular membrane. A further mechanism is suggested within this membrane, which can selectively exchange the $H^+$ and $HCO_3^-$ ions thus formed for other electrolytes, largely $Na^+$ and $Cl^-$ from the plasma. The $Na^+$ and $Cl^-$ ions thus obtained would be then introduced into the interstitial fluid of the nervous system. Because of the relative impermeability of this barrier to free diffusion of electrolytes, a net increase of two osmols of NaCl in the central nervous system interstitial fluid will result from each mol of $CO_2$ thus hydrated and exchanged. Water, which moves freely among all the intracranial compartments (see above), enters from the plasma to establish osmotic equilibrium. Insofar as $Na^+$ and $Cl^-$ are thus transferred into the interstitial fluid and cerebrospinal fluid from the plasma preferentially, at a rate greater in proportion to their plasma concentration than other electrolytes, then the cerebrospinal fluid and interstitial fluid will have a higher NaCl concentration than plasma, but will maintain isotonicity (fig. 3).

This mechanism is hypothesized to exist throughout the entire parenchymal perivascular membrane of the central nervous system, including the choroid plexus, with the exception of the arachnoid villi in the dural sinuses (fig. 4), thus providing a hydrostatic pressure gradient to drive interstitial fluid outward through the pial surface of the nervous system into the subarachnoid space, and cerebrospinal fluid through the ventricular system into the cisterna magna and thence over the convexity of the brain. The net influx of intracranial extravascular electrolytes and water is envisioned as moving into the subarachnoid space and back into the blood stream, largely through the arachnoid villi, at a rate determined by, among other factors, the $CO_2$ production of the central nervous system.

The maximum rate of net extravascular fluid production predicted by this hypothesis can be calculated for man on the assumption that all the $CO_2$ produced by the central nervous system is hydrated and exchanged for NaCl and that the blood-brain barrier is otherwise completely impermeable to $Na^+$ and $Cl^-$. Since it is highly unlikely that either of these conditions is actually achieved, the calculated results would be expected to be high. Accepting a $CO_2$ production of 46 ml per min. by the human brain (91), 13.5 ml per min. of isotonic NaCl could be moved from the plasma into the extravascular compartments. This figure greatly exceeds the generally accepted values for rate of cerebrospinal fluid production (112), and the proposed mechanism is therefore capable of producing the observed water movement.

On the basis of this hypothesis, it is possible to account for the decrease in intracranial fluid formation after acetazoleamide administration in the following manner. Carbonic anhydrase inhibition in the central nervous system allows essentially all of the metabolic $CO_2$ produced by the cells to diffuse freely into the blood plasma before any appreciable hydration to $H^+$ and $HCO_3^-$ has occurred. Therefore, after acetazoleamide inhibition of the intrinsic central nervous system carbonic anhydrase, the $H^+$ and $HCO_3^-$ available for exchange with plasma $Na^+$ and $Cl^-$ diminishes and, since this represents a decreased rate of production of osmotically active particles in the extravascular fluids, the net movement of water from the plasma is proportionately reduced.

This mechanism for the transfer of $Na^+$ across a cellular membrane by exchange for metabolically produced $H^+$ with the accompaniment of osmotically obligate water is essentially identical with that proposed by Pitts (124) for kidney tubular reabsorption

of sodium. In the kidney, however, the 'pump' is oriented to move $Na^+$ and $H_2O$ from the extravascular fluid (glomerular filtrate) into the plasma, whereas in the brain it is proposed to move these substances from plasma into extravascular fluid. Interference by acetazolcamide with this kidney tubular mechanism in a manner entirely analogous to that proposed for intracranial fluid formation is thought to be responsible for the lack of water reabsorption and consequent diuresis produced by this compound (14). Since tubular secretion of $K^+$ in exchange for $Na^+$ can occur in the kidney, and since $K^+$ and $H^+$ behave similarly with respect to the trans-blood-brain barrier electrical potential difference (see above), the possibility of $K^+$ for $Na^+$ exchange across the blood-brain barrier must be considered.

A further consequence of this hypothesis is the prediction that acetazolcamide should decrease the rate of accumulation of parenterally administered radioactive sodium in the central nervous system. That this is indeed the case has been shown by Woodbury *et al.* (168). However, these authors interpret the reduced uptake of radio sodium ($Na^{22}$) by the brain following treatment with acetazolcamide as resulting not from a decrease in blood-brain barrier transport, but rather from decreasing the influx of sodium into brain cells. They assume originally that the brain chloride is extracellular and present in about the same concentration as in plasma, and thus use the chloride space as a measure of extracellular fluid space of brain. They further assume that the concentration of extracellular brain sodium is the same as plasma, and on these two assumptions calculate the ratio of brain extracellular to intracellular sodium. On this basis, these authors state that acetazolcamide markedly decreases intracellular sodium concentration in brain tissue (166). Therefore, the reduced turnover of radiosodium in the brain following acetazolcamide is believed by them to indicate a decreased influx of sodium into the cells and a consequent decrease in intracellular sodium concentration. This decrease in sodium concentration in cells is suggested by these authors as the basis for the general anticonvulsant action not only of acetazolcamide, but also of diphenylhydantoin. Since diphenylhydantoin, unlike acetazolcamide, increases the turnover of radiosodium between plasma and brain while simultaneously decreasing intracellular sodium concentration (using the assumptions mentioned previously), it is proposed that diphenylhydantoin enhances the active extrusion of sodium from brain cells, thereby lowering intracellular brain sodium concentration.

Thus Woodbury (167) de-emphasizes the role of a structural blood-brain barrier separating plasma from central nervous system interstitial fluid and proposes that "the so-called blood-brain barrier is related more to the small volume in which substances distribute rather than to an active extrusion process" (see fig. 1). He apparently considers the environment of the neurons to consist of an aqueous milieu the composition of which is determined by ultrafiltration from the plasma, and by active movement of solutes between the interstitial and intracellular compartment.

How many things are left in an uncertain state for the future!

## REFERENCES


1. Aird, R. *California Med.* 69: 360, 1948.
2. Aird, R. and L. Strait. *A.M.A. Arch. Neurol. & Psychiat.* 51: 54, 1944.
3. Allen, J. N. *A.M.A. Arch. Neurol. & Psychiat.* 73: 241, 1955.
4. Altweiss, C. and J. Magnes. *XX Internat. Physiol. Congr., Abstr.* 1956, p. 21.
5. Amberson, W. R., T. P. Nash, A. G. Mulder and D. Binns. *Am. J. Physiol.* 122: 224, 1938.
6. Andrew, J. and J. Taylor. *Am. J. Physiol.* 193: 207, 1958.
7. Ashby, W., R. F. Garzoli and E. M. Schuster. *Am. J. Physiol.* 170: 116, 1952.
8. Bakay, L. *A.M.A. Arch. Neurol. & Psychiat.* 70: 30, 1953.
9. Bakay, L. *The Blood-Brain Barrier.* Springfield: Thomas, 1956.
10. Bakay, L. and O. Lindberg. *Acta physiol. scandinav.* 17: 179, 1949.
11. Becker, R. A. and R. B. Aird. *J. Cell. & Comp. Physiol.* 46: 127, 1955.
12. Bennhold, H. *Ergebn. inn. Med. u. Kinderh.* 42: 273, 1932.
13. Bering, E. A., Jr. *J. Neurosurg.* 9: 275, 1952.
14. Berliner, R. W., T. J. Kennedy, Jr. and J. Orloff. *Am. J. Med.* 11: 274, 1951.
15. Bertrand, C. *J. Neuropath. & Exper. Neurol.* 11: 53, 1952.
16. Biedl, A. and R. Kraus. *Zentr. inn. med.* 19: 1185, 1898.
17. Bonnet, V. and F. Bremer. *Compt. rend. Soc. de biol.* 126: 1271, 1937.
18. Borell, U. and A. Örström. *Acta physiol. scandinav.* 10: 231, 1945.
19. Brierley, J. B. *J. Neurol. Neurosurg. & Psychiat.* 13: 203, 1950.
20. Broman, T. *The Permeability of the Cerebrospinal Vessels in Normal and Pathological Conditions.* Copenhagen: Munksgaard, 1949.
21. Cestan, R., M. Sendrail and H. Lassale. *Compt. rend. Soc. de biol.* 93: 475, 1925.
22. Cigardo, V. H. and R. Bremier. *Rev. Soc. argent. biol.* 27: 132, 1951.
23. Clemente, C. D., J. Sutin and J. T. Silverstone. *Am. J. Physiol.* 188: 193, 1957.

24. Cloette, M. and H. Fischer. *Arch. exper. Path. u. Pharmakol.* 158: 254, 1930.
25. Collip, J. B. and P. L. Backus. *Am. J. Physiol.* 51: 551, 1920.
26. Coppen, A. J. and G. F. M Russell. *Lancet* 273: 926, 1957.
27. Davenport, H. W. *Physiol. Rev.* 26: 560, 1946.
28. DeBersaques, J. *Arch. internat. physiol.* 63: 1, 1955.
29. Demole, V. *Arch. exper. Path. u. Pharmakol.* 120: 229, 1927.
30. Dempsey, E. W. and G. B. Wislocki. *J. Biophys. & Biochem. Cytol.* 1: 245, 1955.
31. Downman, C. B. B. and C. C. Mackenzie. *Lancet* 2: 471, 1943.
32. Dubner, H. H. and R. W. Gerard. *J. Neurophysiol.* 2: 142, 1939.
33. Dusser de Barenne, J. G., C. S. Marshall, W. S. McCulloch and L. F. Nims. *Am. J. Physiol.* 124: 631, 1938.
34. Ehrlich, P. *Das Sauerstoff-Bedurfnis des Organismus. Eine Farben-analytische Studie.* Berlin, 1885, p. 69.
35. Elliott, K. A. C. *Proc. Soc. Exper. Biol. & Med.* 63: 234, 1946.
36. Elliott, K. A. C. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 54.
37. Elliott, K. A. C., M. E. Grieg and M. P. Benoy. *Biochem. J.* 31: 1003, 1937.
38. Elliott, K. A. C. and H. Jasper. *Am. J. Physiol.* 157: 122, 1949.
39. Farquhar, M. G. and J. F. Hartmann. *J. Neuropath. & Exper. Neurol.* 16: 18, 1957.
40. Feldberg, W. *XX Internat. Physiol. Congr., Abstr. of Rev.* 18, 1956.
41. Flexner, L. B. *Physiol. Rev.* 14: 161, 1934.
42. Flexner, L. B. and J. B. Flexner. *J. Cell. & Comp. Physiol.* 34: 115, 1949.
43. Folch,. J. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 133.
44. Friedmann, U. *Physiol. Rev.* 22: 125, 1942.
45. Friedmann, U. and A. Elkeles. *Ztschr. ges. exper. Med.* 80: 212, 1932.
46. Fries, B. A. and I. L. Chaikoff. *J. Biol. Chem.* 141: 469, 479, 1941.
47. Fries, B. A., G. W. Changus and I. L. Chaikoff. *J. Biol. Chem.* 132: 23, 1940.
48. Frostig, J. P. *Am. J. Psychiat.* 96: 1167, 1940.
49. Geiger, A. *Physiol. Rev.* 38: 1, 1958.
50. Geiger, A., J. Magnes and R. S. Geiger. *Nature, London* 170: 754, 1952.
51. Geiger, A. and S. Yamasaki. *J. Neurochem.* 1: 93, 1956.
52. Gellhorn, E. and M. Kessler. *A.M.A. Arch. Neurol. & Psychiat.* 49: 808, 1943.
53. Gerard, R. W. *Cold Spring Harbor Symp. Quant. Biol.* IV: 292, 1936.
54. Gibbs, F. A., E. L. Gibbs, W. G. Lennox and L. F. Wimms. *J. Aviation Med.* 12: 1, 1941.
55. Goldmann, E. E. *Vitalfarbung am Zentralnervensystem.* Berlin: Reimer, 1913.
56. Goldsworthy, P. D., R. B. Aird and R. A. Becker. *J. Cell. & Comp. Physiol.* 44: 519, 1954.
57. Grazer, F. M. and C. D. Clemente. *Proc. Soc. Exper. Biol. & Med.* 94: 758, 1957.
58. Greenberg, D. M., R. B. Aird, M. D. D. Boelter, W. W. Campbell, W. E. Cohn and M. M. Murayama. *Am. J. Physiol.* 140: 47, 1943.
59. Grenell, R. G. and P. W. Davies. *Fed. Proc.* 9: 52, 1950.
60. Gröntoft, O. *Acta path. et microbiol. scandinav.* Suppl. C, 1954.
61. Gruner, J., S. S. Sung, M. Tubiana and J. Segarra. *Compt. rend. Soc. de biol.* 145: 203, 1951.
62. Gurdian, E. S., J. E. Webster and W. E. Stone. *A. Res. Nerv. & Ment. Dis., Proc.* 26: 184, 1947.
63. Hahn, L. and G. Hevesy. *Acta physiol. scandinav.* 1: 347, 1940.
64. Hastings, A. B. and C. B. Huggins. *Proc. Soc. Exper. Biol. & Med.* 30: 458, 1933.
65. Hauptmann, A. *Deutsche Ztschr. Nervenh.* 89: 53, 1926.
66. Hauptmann, A. and W. Gärtner. *Ztschr. ges. Neurol. Psychiat.* 140: 572, 1932.
67. Havgaard, N., M. Vaughan, E. S. Havgaard and W. J. Stadie. *Biol. Chem.* 208: 549, 1954.
68. Hele, M. D. *Biochem. J.* 55: 864, 1953.
69. Heppenstall, M. E. and G. D. Greville. In: *Electroencephalography.* London: Macdonald, 1950, p. 152.
70. Herlin, L. *Nord. med.* 51: 137, 1954.
71. Herlin, L. *Acta physiol. scandinav.* 37: Suppl. 127, 1956.
72. Hess, A., *A.M.A. Arch. Neurol. & Psychiat.* 73: 380, 1955.
73. Hess, A. *J. Comp. Neurol.* 102: 67, 1955.
74. Hestrin-Lerner, S. and B. Shapiro. *Biochem. et biophys. acta* 12: 553, 1954.
75. Hestrin-Lerner, S. and B. Shapiro. *Biochem. et biophys. acta* 13: 54, 1954.
76. Himwich, H. E. *Brain Metabolism and Cerebral Disorders.* Baltimore: Williams & Wilkins, 1951.
77. Himwich, H. E. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 551.
78. Himwich, H. E. *Progr. Neurol. and Psychiat.* 10: 16, 1955.
79. Himwich, W. A., J. C. Petersen and M. L. Allen. *Neurology* 7: 705, 1957.
80. Hoagland, H., H. E. Himwich, E. Campbell, J. F. Fazekas and Z. Hadidian. *J. Neurophysiol.* 2: 276, 1939.
81. Hodgkin, A. L. *Biol. Rev.* 26: 339, 1951.
82. Hoff, H. *Med. Klin. (Munich)* 29: 112, 1933.
83. Horsten, G. P. M. and P. J. Klopper. *Arch. internat. physiol.* 60: 491, 1952.
84. Huggins, C. B. and A. B. Hastings. *Proc. Soc. Exper. Biol. & Med.* 30: 459, 1933.
85. Hunter, F. E., Jr. and O. H. Lowry. *Pharmacol. Rev.* 8: 89, 1956.
86. John, E. R., B. M. Wenzel and R. D. Tschirgi. *J. Physiol.* 146: 550, 1959.
87. Kahn, J. B. *Current Res. in Anesth. & Analg.* 29: 273, 1950.
88. Katzenelbogen, S. *The Cerebrospinal Fluid and its Relation to the Blood: A Physiological and Clinical Study.* Baltimore: Johns Hopkins Press, 1935.
89. Katzman, R. and P. H. Leiderman. *Am. J. Physiol.* 175: 263, 271, 1953.
90. Kerr, S. E., C. W. Hampel and M. J. Ghantus. *J. Biol. Chem.* 119: 405, 1946.
91. Kety, S. S. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 20.
92. Kister, S. J. *J. Pharmacol. & Exper. Therap.* 117: 402, 1956.
93. Klein, J. R., R. Hurvitz and N. S. Olsen. *J. Biol. Chem.* 164: 509, 1946.
94. Klein, J. R., R. Hurvitz and N. S. Olsen. *J. Biol. Chem.* 167: 1, 1947.
95. Knapp, L. M., J. R. Atkinson and A. A. Ward. *Neurology* 7: 119, 1957.
96. Koenigstern, H. *J. Invest. Dermat.* 17: 99, 1951.

97. Krebs, H. A., L. V. Eggleston and C. Terner. *Biochem. J.* 48: 530, 1951.
98. Krogh, A. *Proc. Royal Soc., London. ser. B* 133: 140, 1946.
99. Leusen, I. R. *Arch. internat. physiol.* 58: 115, 1950.
100. Leusen, I. R. *J. Physiol.* 110: 319, 1950.
101. Leusen, I. R. *Am. J. Physiol.* 176: 39, 45, 513, 1954.
102. Levine, R. and M. S. Goldstein. *Brookhaven Symp. Biol.* 5: 73, 1952.
103. Lewandowsky, M. *Ztschr. klin. Med.* 40: 480, 1900.
104. Libet, B. and R. W. Gerard. *J. Neurophysiol.* 2: 153, 1939.
105. Lindberg, O. and L. Ernster. *Biochem. J.* 46: 43, 1950.
106. Long, C., S. Ochoa and R. A. Peters. *J. Physiol.* 96: 5, 1939.
107. Louran, M. *Compt. rend. Soc. de biol.* 238: 842, 1954.
108. Maddock, S., J. E. Hawkins and E. G. Holmes. *Am. J. Physiol.* 125: 551, 1939.
109. Manery, J. R. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 124.
110. Manery, J. F. and W. F. Bale. *Am. J. Physiol.* 132: 215, 1941.
111. Manery, J. F. and L. F. Haege. *Am. J. Physiol.* 134: 83, 1941.
112. Masserman, J. H. *A.M.A. Arch. Neurol. & Psychiat.* 32: 523, 1934.
113. Mayer-Gross, W. E. and J. W. Walker. *Biochem. J.* 44: 92, 1949.
114. Maynard, E. A., R. L. Schultz and D. C. Pease. *Am. J. Anat.* 100: 409, 1957.
115. Meltzer, S. J. *Am. J. Physiol.* 3: ix, 1899–1900.
116. Miller, W. H., A. M. Dessert and R. O. Roblin, Jr. *J. Am. Chem. Soc.* 72: 4893, 1950.
117. Mullins, F., A. B. Hastings and W. M. Lees. *Am. J. Physiol.* 121: 719, 1938.
118. Noonan, T. R., W. O. Fenn and L. Haege. *Am. J. Physiol.* 132: 474, 1941.
119. Olsen, N. S. and J. R. Klein. *Arch. Biochem.* 13: 343, 1947.
120. Olsen, N. S. and G. G. Rudolph. *Am. J. Physiol.* 183: 427, 1955.
121. Park, J. T. and J. L. Strominger. *Science* 125: 99, 1957.
122. Patek, P. H. *Anat. Rec.* 88: 1, 1944.
123. Pease, D. C. *Anat. Rec.* 121: 701, 1955.
124. Pitts, R. F. *Am. J. Med.* 9: 356, 1950.
125. Resnik, H., M. F. Mason, R. T. Terry, C. Pilcher and T. R. Harrison. *Am. J. M. Sc.* 191: 835, 1936.
126. Rivkine, A. *Arch. internat. physiol.* 57: 245, 1950.
127. Rodriguez-Peralta, L. A. *J. Comp. Neurol.* 102: 27, 1955.
128. Rodriguez-Peralta, L. A. *J. Comp. Neurol.* 107: 455, 1957.
129. Roux, E. and A. Borrel. *Ann. Inst. Pasteur* 12: 225, 1898.
130. Rubin, M. A., H. E. Hoff, A. W. Winkler and P. K. Smith. *J. Neurophysiol.* 6: 23, 1943.
131. Sabbatini, L. *Riv. sper. freniat.* 27: 946, 1901.
132. Sacks, J. and G. G. Culbreth. *Am. J. Physiol.* 165: 251, 1951.
133. Sakel, M. Pharmacological treatment of schizophrenia in *Nervous and Mental Disease.* New York and Washington: Monograph Series, No. 62, 1938.
134. Schaltenbrand, G. and P. Bailey. *J. Psychol. u. Neurol.* 35: 199, 1928.
135. Schultz, R. L., E. A. Maynard and D. C. Pease. *Am. J. Anat.* 100: 369, 1957.
136. Soloman, A. K. *J. Clin. Invest.* 28: 1297, 1949.
137. Spatz, H. *Arch. Psychiat.* 101: 267, 1933.
138. Stern, L. *Brit. M. J.* 2: 538, 1942.
139. Stern, L. *Lancet* 2: 572, 1942.
140. Stern, L. and G. J. Chvoles. *Compt. rend. Soc. de biol.* 112: 568, 1933.
141. Stern, L. and R. Gautier. *Arch. internat. de Physiol.* 17: 391, 1922.
142. Strominger, J. L. *J. Biol. Chem.* 224: 532, 1957.
143. Sugar, O. and R. W. Gerard. *J. Neurophysiol.* 1: 558, 1938.
144. Swanson, A. G., L. S. Stavney and F. Plum. *Neurology* 8: 787, 1958.
145. Sweet, W. H., B. Selverstone, S. Soloway and D. Stetten, Jr. *Surgical Forum, American College of Surgeons.* Philadelphia: Saunders, 1951, p. 376.
146. Tschirgi, R. D. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 34.
147. Tschirgi, R. D. In: *Biology of Neurologia,* edited by W. F. Windle. Springfield: Thomas, 1958, p. 130.
148. Tschirgi, R. D., R. R. Frost and J. L. Taylor. *Proc. Soc. Exper. Biol. & Med.* 87: 373, 1954.
149. Tschirgi, R. D., K. Inanaga, J. L. Taylor, R. M. Walker and R. R. Sonnenschein. *Am. J. Physiol.* 190: 557, 1957.
150. Tschirgi, R. D. and J. L. Taylor. *Am. J. Physiol.* 195: 7, 1958.
151. van Harreveld, A. and S. Ochs. *Am. J. Physiol.* 187: 180, 1956.
152. Verzar, F. and E. T. McDougall. *Absorption from the Intestine.* London: Longmans, 1936.
153. von Angyal, L. *Ztschr. ges. Neurol. Psychiat.* 157: 35, 1937.
154. von Euler, U. S. *Skandinav. Arch. Physiol.* 80: 94, 1938.
155. Waelsch, H. B. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 106.
156. Walker, S. M., E. A. Smolik and A. S. Gilson, Jr. *Am. J. Physiol.* 145: 223, 1945.
157. Wallace, G. B. and B. B. Brodie. *J. Pharmacol. & Exper. Therap.* 60: 397, 1937.
158. Wallace, G. B. and B. B. Brodie. *J. Pharmacol. & Exper. Therap.* 65: 214, 1939.
159. Walter, F. K. *Arch. Psychiat.* 101: 195, 1933.
160. Weed, L. H. *Am. J. Anat.* 31: 191, 1923.
161. Weed, L. H. *Am. J. Anat.* 32: 253, 1923.
162. Weil-Malherbe, H. *Biochem. J.* 30: 665, 1936.
163. Windle, W. F. (editor). *Biology of Neuroglia.* Springfield: Thomas, 1958.
164. Wislocki, G. B. and L. S. King. *J. Comp. Neurol.* 96: 371, 1952.
165. Wolff, P. H. and R. D. Tschirgi. *Am. J. Physiol.* 184: 220, 1956.
166. Woodbury, D. M. *J. Pharmacol. & Exper. Therap.* 115: 74, 1955.
167. Woodbury, D. M. In: *Biology of Neuroglia,* edited by W. F. Windle. Springfield: Thomas, 1958, p. 120.
168. Woodbury, D. M., A. Koch and A. Vernadakis. *Neurology* 8, Suppl. 1: 113, 1958.
169. Yannet, H. *Am. J. Physiol.* 128: 683, 1940.
170. Zand, N. *Les Plexus Choroïdes.* Paris: Masson, 1930.

# Abnormalities of neural function in the presence of inadequate nutrition

JOSEF BROŽEK[1]
FRANCISCO GRANDE

*Laboratory of Physiological Hygiene, School of Public Health, University of Minnesota, Minneapolis, Minnesota*

CHAPTER CONTENTS



ALTERATION OF METABOLISM induced by nutritional means, frequently requiring a considerable investment of time and rigorous dietary control, has not often appealed to neurophysiologists as an experimental procedure. Consequently, the effect of defective nutrition on the nervous system has received relatively little systematic attention (87) even though a variety of neurological syndromes has been recognized as nutritional in origin, the essential 'lesions' being biochemical in character (258, p. 787).

The investigations of metabolism and nervous function have suffered because no adequate indexes of *in vitro* function are available for the central nervous system. *In vivo*, the electrical manifestations provide useful but limited information. The technique of conditioned responses and the behavioral indexes have been used in nutritional research, but not systematically (30, 48). Performance capacity, assessed quantitatively in animals, deserves more attention than it has received in the past (27, 301). In man a large number of studies on nutritional deficiencies were stimulated by interest in 'fitness' and the changes in fitness under physiological stresses of nutritional origin. For this reason the 'higher,' more complex functions (intellectual, psychomotor) were emphasized (28) rather than simpler functions involving chronaxie or tendon reflex studies.

Nutritional deficiencies may disturb the normality of nervous function either directly by interfering with

[1] Present address: Department of Psychology, Lehigh University, Bethlehem, Pennsylvania.

neural metabolism (through producing low blood sugar or a deficiency of some vitamin), or indirectly by routes such as disproportionate bone growth (as in vitamin-A deficient pups). Nutritional deficiencies result in a variety of lesions in the brain, spinal cord and peripheral nerves (77), including the destruction of the myelin sheaths of nerve fibers (223, p. 700). Many of these changes are not specific. Thus demyelination was reported in conditions varying from starvation alone (in rats) through deficiencies of pantothenic acid and pyridoxine (in chicks, mice and pigs) to copper deficiency (in lambs).

The existence of large differences in the rate of oxygen consumption in different parts of the nervous system and the species differences in nutritional requirements complicate the assessment of neurophysiological responses to dietary deficiencies. Thus, the respiration of the brain cortex is some 30 times greater than that of the peripheral nerves (86), and within the central nervous system of the adult there is a fairly steep quantitative metabolic gradient from cerebral cortex to brain stem, cerebellum and medulla (106, p. 164).

In nutritional deficiencies the alterations of nervous function depend on the duration of the deficiency and the magnitude of the difference between the amount of nutrient available and the physiological requirement for it. This accounts, in part, for the differences between results reported by different investigators. From the practical point of view the time parameter is very important. Nutritional deficiencies that require months to produce symptoms are of no concern in evaluating performance capacity of men maintained for a few days on emergency rations, while they may be of crucial importance for populations on chronically deficient diets.

In addition to alterations of nervous function resulting from nutritional deficiencies, it is necessary to consider also abnormalities, nutritional in origin but not caused by deficiencies, such as the spastic paralysis of lathyrism.

### ACUTE STARVATION

From the point of view of dietary control, acute starvation (complete withdrawal of food with free access to water) is the simplest nutritional deficiency. At the same time it is perhaps the most complex one metabolically. In the older literature (182, p. 223) a variety of histological changes in the nervous system were reported and interpreted as degenerative alterations resulting from inanition. Liu & Windle (149), however, found that brains of starved guinea pigs differed from those of control animals in surprisingly few details, among which were reduced amounts of Nissl substance in some of the large nerve cells of the brain stem.

An exploratory study with starved and subsequently re-fed guinea pigs suggested that the retention of a learned task (running an alteration maze) was not impaired (149). Total food deprivation increases for a time the general activity of an animal, as measured in rats by means of revolving drums (72). In dogs withdrawal of food for 4 to 6 days results in diminished sexual interest, shortened duration of sexual conditioned reflexes with increase of latent period, and a partial or complete loss of conditioned ejaculation (81).

Around the turn of the century, various 'hunger artists' went through prolonged fasts with surprisingly unimpressive signs of deterioration (138). In contrast to these men who kept their energy expenditure at a low level, marked changes were found in young men undergoing 4 days of starvation combined with hard physical work (105). In regard to their manipulative performance (29), statistically highly significant deterioration was noted in tests of speed and of coordination. Interestingly enough, there was no decrement in hand grip and the decrements in back pull did not reach a level of statistical significance. Body sway increased substantially. Tests of intellectual functions showed little or no impairment. The principal subjective symptoms and complaints included tiredness, 'weakness' (not demonstrated by strength measurements) and decreased ability to concentrate. The men felt sleepy and their self-initiated activities decreased. Nausea was a common complaint after the exhausting runs on the treadmill. In spite of the availability of water, the men complained of dryness of the throat.

From the metabolic point of view, the alterations that may account for the initial changes in nervous and motor function include the lowering of blood sugar, ketosis and dehydration (270). In advanced diabetes, with acidosis and ketosis, a profound (40 per cent) reduction in cerebral utilization of oxygen takes place in the presence of undiminished cerebral blood flow and a normal arterial oxygen saturation (130). The accumulation of ketone bodies in the blood of individuals in the advanced state of starvation may lead to a severe disturbance of cerebral metabolism and function.

SEMISTARVATION

Semistarvation, the prolonged caloric restriction characteristic of famines, has been for ages past the most important type of nutritional deficiency. Much of the literature on this subject was summarized in connection with the presentation of experimental observations made in the course of World War II (133, p. 689).

Important neurophysiological data were obtained after World War I when food supplies in Petrograd became grossly inadequate. The effects on the functioning of the central nervous system of dogs were studied using Pavlov's technique of conditioned reflexes (80, 224). As in other dietary stresses (cf. 82), one of the early neurophysiological symptoms of semistarvation was the loss of differential inhibition. In the next stage, well-established conditioned responses, elicited under standard conditions, decreased in intensity. The reactivity of the central nervous system was lowered and it became impossible to elaborate new conditioned responses. In time responses to previously conditioned artificial stimuli, such as the sound of a bell, decreased and finally could not be elicited, while the responses to natural conditioned stimuli, such as the sight or odor of food, were still retained in considerable force. In the terminal phase of semistarvation even these responses were greatly reduced. The unconditioned salivary reflex continued to function throughout, although the intensity of the response was depressed.

American authors (6, 225) who have produced bodily stunting by a quantitatively inadequate diet, even when started before weaning (19), found no significant impairment of maze learning ability.

There are many reports on behavior under conditions of 'natural' starvation (47; 104, p. 235; 133, p. 783). Plaut (212) differentiates three stages: chronic fatigue, occasional apparent and temporary improvement (adaptation), and 'psychic cachexia.' Leyton (145), writing on the basis of his experience in German camps for prisoners of war, pointed out that the reactions to the reduction of diet from that of the frontline soldier to the meager camp fare could be divided into many stages. At first there is a loss of the natural feeling of well-being. With time, hunger increases in intensity until all thought becomes concentrated on food. Next comes a progressive physical and mental lethargy. Endurance was markedly decreased. Polyuria became severe. Muscular action became progressively slower, with signs of exceedingly slow cerebration in advanced inanition. Sexual desire was reduced while desire for tobacco greatly increased. Standards of cleanliness were lowered and pride in personal appearance lost. Moral standards deteriorated. Physical examination revealed sluggish tendon reflexes. The sight remained good, except for rare cases of mild night blindness. Hearing was normal or acute. Sensations of touch and temperature were not impaired.

In advanced semistarvation (104, p. 174) the musculature becomes extremely atrophied. Adynamia, myalgia and gastrocnemic cramps are prominent symptoms. The terminal phase is characterized by reduction and retardation of all mental processes, with oligokinesia and bradykinesia, oligomimics and bradylalia (104, p. 252). Quantitative observations on changes in the basic aspects of nervous function in man are very limited. Marked increases in vestibular chronaxia were reported (49) in emaciated men.

According to Russian observations on semistarvation made in World War II (216), the motor adynamy results from lack of energy-yielding substances, decreased muscle mass, alterations in the activity of motor nervous centers and possibly other factors. Physical exertion leads rapidly to exhaustion which may pass into coma. In advanced stages the sensory thresholds are increased and pain sensitivity is diminished. The reaction of the pupils to light is weak, the arterial pressure low, the pulse slow, the bowels constipated and the adrenals atrophied. In regard to psychic alterations (1), asthenia was considered the principal syndrome in advanced semistarvation, characterized by sluggish intellectual processes, decreased ability to concentrate and incapacity for sustained mental effort. There is a lowering of all higher interests and feelings, and a tendency to daydreaming. Both irritability and restlessness, and apathy, bordering on abulia, are present. Some patients exhibit character disorders such as sullenness, obstinacy or lack of tact. Psychoses were rare even at the height of the Leningrad famine (cf. 32). Hallucinations and other psychotic symptoms were present mostly in those cases in which caloric deficiency was complicated by pellagra, infection or trauma.

The symptoms of 'natural' semistarvation were produced under controlled conditions (133) in a study in which initially normal young men lost one fourth of their initial body weight in the course of 24 wk. Sensory functions (133, p. 675) were remarkably resistant to this nutritional stress. Visual threshold remained unaltered. The acuity of hearing actually increased—a small change that was reversed in the

course of nutritional rehabilitation. Clinical examination of the neurological status yielded largely negative results. There was no impairment in the sense of vibration. Skin sensitivity remained normal, except for three men who developed mild paresthesias. The patellar and the Achilles tendon reflexes were diminished.

The components of the capacity for brief neuromuscular performance—strength, speed and coordination—were examined by a battery of tests. Changes in all these functions were statistically highly significant. However, there were substantial differences in the relative amount of deterioration as indicated by the displacement ratio (difference divided by the standard deviation of the control values). The largest change took place in the strength measurements in which the peripheral factors (size and state of the muscles) limited performance. Performance on tests in which the central nervous system was the critical component, such as the speed of tapping, changed but little. The pattern-tracing, a complex task involving eye-hand-foot coordination and performed while the subjects were walking on a treadmill, was intermediary in regard to the relative amount of deterioration.

Measured intellectual performance did not change importantly in spite of subjective complaints about inability to concentrate and the difficulty in developing thoughts. Using 'speed tests' of intelligence in which the working time was short and strictly limited, no statistically significant decrement was observed in perception of spatial relations, word fluency, short-term memory, inductive reasoning or perceptual speed. In the 'power tests' with no rigid time limits imposed and actual working times of 8 to 10 hr., the total scores showed a minimal decrement at the end of the semistarvation period. This was in sharp contrast to a marked decline in spontaneous mental effort and achievement which only gradually returned to 'normal' on refeeding. In the psychometric study of personality, a marked rise was present on the Hypochondriasis, Depression and Hysteria scales of the Minnesota Multiphasic Personality Inventory (132, 231).

## PROTEIN DEFICIENCY

In contrast to the liver, which suffers a large loss of protein during stravation, the brain shows only a very small change in protein content under the same conditions (2). Liver enzymes are depleted during protein deficiency (173, 285), but we were unable to secure information concerning changes in brain enzymes.

Deficiency of some amino acids is known to produce alterations of nervous function. Valine-deprived rats became extremely sensitive to touch and developed a severe incoordination of movements (222). The animals walked with a staggering gait and frequently exhibited a rotary motion which continued until they fell to the cage floor from sheer exhaustion. Later, degenerative changes in the spinal cord were reported (70).

Dogs on a gliadin diet deficient in lysine developed neurological manifestations resembling those observed in 'canine hysteria' (169). Lysine was found to be helpful in preventing the attacks in dogs fed a diet of baked meat scraps and wheat flour (8).

In research on amino acids and nervous function, most attention has been devoted to glutamic acid and its amide, substances appearing in high concentration in the central nervous system. Glutamic acid can serve as a substrate for oxidative processes in nerve tissues under conditions of insufficient glucose supply, such as insulin hypoglycemia. Nutritionally, glutamic acid is classified as a nonessential amino acid, readily synthesized in mammalian organisms. Furthermore, it is contained in substantial amounts in animal and vegetable proteins. In the majority of clinical studies on the effects of glutamic acid administration, little or no attention has been paid to the amount of glutamic acid provided in the diet. Patients given supplements of glutamic acid are expected, then, to benefit from the addition of limited amounts of a substance which is provided, in relatively large quanties, in the dietary proteins. It is perhaps not surprising, under these conditions, that well-controlled studies on the effects of glutamic acid on intelligence tend to yield negative results (193, 194).

The mechanism of improvements reported in some studies, beyond the range of random fluctuations, is uncertain. They may represent a real improvement in intelligence or a better utilization of existing intellectual abilities through improved emotional control. Waelsch (283) favored the second alternative. He commented that a valid appraisal of the value of glutamic acid supplementation will require a better differentiation of the types of mental defectives.

### *Kwashiorkor*

The term, with a variety of equivalents in other areas, refers to protein malnutrition seen in African

children, making them dull and apathetic. Carothers (36, p. 111) believes that the arrest of mental development at the age of 2 to 4 years is unlikely to be completely remedied in later years. Even children who are not severely ill are remarkably silent and still (275, p. 100). They seem to have lost all normal curiosity and, in advanced stages of the disease, they are hopelessly apathetic, showing only the responses of resentment and pain. The behavior is considered as the best single guide to the degree of severity of the disease. As to neuropathology, cerebral edema and congestion is frequent, but the brain has not been studied in detail and the histological counterpart, if any, of the mental changes is not known (275, p. 155).

### DEHYDRATION

Water deprivation, much as the deprivation of calories and some essential nutrients, markedly affects behavior long before any clear changes take place in the capacity of the nervous system to function normally. Thus general activity is substantially elevated when rats are deprived of water, with food available ad libitum (73).

According to Morgulis (182), severely dehydrated animals have hyperemic changes in the brain and spinal cord, but on the basis of available information it is not easy to determine a causal relationship between dehydration and the nervous alterations. Although water is held in the nervous substance with great tenacity, even when the rest of the body is dehydrated (243, p. 34), dehydration produces a variety of important functional alterations in the body, affecting the composition and the distribution of body fluids, the circulation, and temperature regulation, which may cause the neural manifestations seen in this state.

The descriptions of signs and symptoms of dehydration in man are based on observations in children suffering from severe diarrhea and in patients with cholera and extensive burns, as well as in men lost in the desert and in shipwreck survivors. In modern times the work of Adolph and his co-workers provided valuable information on this problem (3).

McGee (163) distinguished five periods (clamorous, cotton-mouth, swollen tongue, shriveled tongue and blood sweat) corresponding to different degrees of dehydration resulting from a water deficit of 2 to 20 per cent of the initial body weight. Besides thirst, which is the first and obvious subjective symptom of dehydration, changes in behavior—apathy, impatience and sleepiness—appear early. Temperamental types are exaggerated; "serious people became positively sombre while others, normally cheerful, exhibited a somewhat hollow vivacity" (23). The subjects were capable of performing estimations and computations but their power to concentrate was impaired.

When the degree of dehydration exceeds 10 per cent loss of the original body weight (corresponding to the last three stages of McGee's classification), more serious manifestations develop, including delirium, spasticity and inability to walk. Perception is greatly impaired, and deafness and blindness may develop. In the terminal stages stupor and unconsciousness dominate the clinical picture.

Under conditions of shipwreck an inadequate stock of drinking water constitutes, after cold, the most distressing and dangerous hardship (43). Thirst, the dominant subjective symptom of dehydration, increases in intensity until it may completely overshadow the discomforts of hunger, cold, pain of wounds or sores, and fatigue. Severe dehydration, frequently complicated by sea-water poisoning, results in blurred consciousness, illusions and hallucinations, and, finally, in delirium and death. Analysis of reports concerning shipwrecked seamen indicates that the effects of drinking sea water are almost invariably disastrous (160).

### MINERALS

Minerals are required by the nervous system principally for *a*) regulation of excitability (Ca, Mg, Na, K), *b*) activation of enzyme systems (Mg, Mn), and *c*) maintenance of structure (Cu). Present information on electrolytes and nervous excitability and conduction was summarized by Keynes & Lewis (131). Recent work has extended our knowledge concerning the role of calcium and magnesium ions in neuromuscular transmission with special reference to acetylcholine release (52, 53). Similar studies have been made on the perfused sympathetic ganglion (54, 68, 117).

#### *Sodium Chloride*

Heat cramps are well known as a symptom of salt deficiency and their prevention by administration of salt is firmly established (57, p. 82); but our understanding of the etiology is still incomplete. In man lassitude and apathy are also produced (155, p. 40).

Salt deficiency causes nervous dysfunction, not only in acute deprivation but also under chronic conditions producing low concentration of salt in the blood. Hypochloremia is associated with headache, dizziness, tremor, hyperreflexia, hyperhydrosis, nervousness, apprehension, restlessness, insomnia, loss of 'pep' and strength, depression, personality changes, and anxiety (228).

*Calcium*

Extracellular calcium is necessary for the preservation of the selective permeability of cell membranes, the ease with which sodium and potassium cross the nerve membrane being reduced by increased calcium level (131, p. 451). Accordingly, lowering of calcium concentration results in greater excitability and a tendency to repetitive discharges on stimulation. Tetany develops in rats on a low calcium and high phosphorus diet, deficient in vitamin D and resulting in rickets with low plasma calcium (26, 244, 248). In man tetany occurs when there is a low concentration of ionized plasma calcium. Primary calcium deficiency in man is probably very rare (253). Tetany has also been reported during periods of semistarvation (232) and spontaneous muscle cramps have been observed in undernourished children (221).

*Magnesium*

Magnesium is necessary as activator of various enzyme systems, including choline acetylase (135). Perhaps the first demonstration of neurophysiological relevance of magnesium was the discovery of the depressing effect of magnesium salts on the nervous system (170, 206). Magnesium concentration of 5 mg per 100 ml of serum produces mild sedation, while profound coma results when the concentration reaches the level of 18 to 21 mg per 100 ml (188). The effects of this metal on muscular activity may be explained as a blocking at the neuromuscular junction (107). The narcotic effects of magnesium on the central nervous system are abolished by the injection of calcium salts (171).

Nutritional deficiency of magnesium causes cattle to become nervous and restless, and to lose appetite. In a more advanced state they develop convulsions and coma, and die (58, 247). In rats the main signs are increased nervous excitability and convulsions, followed by death (136, 137). Similar symptoms were reported in the dog (109; cf. also 21, 24, 99). Barron *et al.* (10) found magnesium deficiency in the rat and the rabbit to result in chromatolysis and degeneration of the Purkinje cells of the cerebellum.

Effects of magnesium deficiency on nervous functions in man are still not well established. In 1944 Miller (172) described a case of tetany due to deficiency of magnesium, and the name of 'magnesium tetany' is found in the literature. Recently Flink and his associates (76) reported finding tremor and delirium in patients who received parenteral fluids for a long time and in chronic alcoholics; in both groups low levels of serum magnesium were found and the administration of magnesium salts gave relief. However, a recent paper (74) contains a description of two cases of magnesium deficiency experimentally produced in man, with no mention of neurologic or psychiatric manifestations.

An interesting aspect of the effects of magnesium on the nervous system is the antagonistic action of potassium. Potassium salts relieve the narcotic effect of magnesium, while the administration of magnesium lowers the serum level of potassium (250, 251).

*Manganese*

Manganese is known to act as an activator of some enzyme systems and is considered a dietary essential for higher animals and man. Manganese deficiency produces alterations of growth, bone development and reproduction. In some animal species certain alterations of nervous function are noted. In the rat there is loss of equilibrium and incoordination of movements (241). In the pig, weakness of the legs has been noted (129, 174) and more recently it was reported (213) that sows maintained on a manganese-deficient diet gave birth to small, weak pigs unable to stand or to walk normally.

*Iodine*

Iodine is the only trace element that is essential for the proper functioning of an endocrine gland, the thyroid. Deficiency of dietary iodine results in an impaired production of thyroid hormone. Uncorrected hypothyroidism results in retarded mental development of the child, and in mental dullness and apathy in the adult. Neurophysiologically, the depressed function of the central nervous system is manifested in the impaired ability to form conditioned reflexes (83). However, impaired intelligence is not a necessary concomitant of acquired hypothyroidism (177).

*Cobalt*

Signs of cobalt deficiency appear to be limited to ruminants which need this trace element as a constituent of vitamin $B_{12}$, (277, p. 147). Failure of appetite is an early and conspicuous symptom, and results in extreme wasting. The mechanism involved in the depression of appetite is not known. Anemia is a later symptom which becomes progressively more severe and the condition, if untreated, is likely to be fatal.

Cobalt has a protective action in a disease of sheep and cattle called 'Phalaris staggers' in which a marked incoordination of gait (staggers) and muscular tremors are the characteristic symptoms, and which develops in some areas where the animals graze predominately on the grass *Phalaris tuberosa*. The structural defect consists of demyelination of nerve fibers of the spinal cord and medulla oblongata (161).

*Copper*

Symptoms similar to those of cobalt deficiency, ranging from spasticity to complete paralysis, were reported in lambs from ewes pastured on lands deficient in copper (156, p. 89). The structural lesions involve a diffuse demyelination of the central nervous system and of the motor tracts of the spinal cord.

VITAMINS

*Thiamine*

Thiamine, as thiamine pyrophosphate and in association with lipoic acid (in the form of lipothiamide pyrophosphate), is a catalyst which plays a central role in pyruvate oxidation. Addition of thiamine (84) or of diphosphothiamine (cocarboxylase) increases the oxygen consumption of the brain tissue of $B_1$-deficient animals (195).

It is still unsettled as to whether the functional alterations of the nervous system are due to the interruption of energy supply or to the accumulation of intermediaries or to both. Peters (208) favored the idea that the former represents the primary event in the production of the nervous symptoms of thiamine deficiency. Other authors believe that the accumulation of pyruvic acid may be the cause of at least some of the signs of the deficiency state, such as anorexia (246). Other intermediary metabolites may accumulate during thiamine deficiency, such as methylglyoxal (226, 281). The fact that the signs of deficiency are aggravated by diets rich in carbohydrate may speak in favor of the pyruvate mechanism. On the other hand, the lack of toxicity of pyruvic acid (209), and the lack of parallelism between the changes in pyruvate concentration in blood and the signs of deficiency (51), make the role of pyruvic acid somewhat doubtful. Extensive work on the participation of thiamine in the transmission of the nervous impulse in the peripheral nerve has been carried out (175, 282).

MANIFESTATIONS OF VITAMIN $B_1$ DEFICIENCY IN ANIMALS. The classic picture of polyneuritis, produced in pigeons and other birds when fed a diet consisting of polished rice, begins with unsteady gait and weakness which progresses until the animal is no longer able to stand. Opisthotonus and convulsions are a characteristic feature that can be reversed within 30 min. by the injection of thiamine into the subarachnoid space (209).

Experimental production of polyneuritis gallinarum in birds fed polished rice involves deficiency of other vitamins besides $B_1$. Moreover, since anorexia is one of the principal and more constant signs of thiamine deficiency, it is clear that starvation may be an aggravating factor. The speed with which the deficiency develops is also an important factor, and differences in symptomatology are observed between the acute and the chronic deficiencies. Also, the presence of other nutrients in the diet may change the pathology of thiamine deficiency to a considerable extent (4). A summary of neurologic symptoms observed in several species is presented in table 1.

The signs of thiamine deficiency can be produced by feeding thiamine-deficient diets, by the presence of thiaminase in food [e.g. Chastek paralysis of the fox (98)] or by feeding analogues of thiamine (300). The peripheral nerves and the proprioceptive nerve endings are functionally normal, as shown by records of nerve action potentials (39). Although some French workers have reported changes of chronaxie in thiamine deficient pigeons (184, 185), the conduction of nervous impulses in peripheral nerves has been found normal in thiamine deficient cats (15). The neurologic signs of thiamine deficiency appear to be related to alterations in the central nervous system, especially the vestibular nuclei.

The question of lesions in the peripheral nerves has been a matter of lively controversy (164, 246). Mannell & Rossiter (154) did not find chemical signs of myelin degeneration in the rat under condi-

TABLE 1. *Neurologic Signs of Thiamine Deficiency in Animals*

| Animal | Signs | References |
|---|---|---|
| Pigeon and chick | Leg weakness, ataxia, opisthotonus, convulsions; paralysis in chronic deficiency (pigeon) | 66, 209, 266, 268 |
| Cat | Ataxia, abnormal posture, swaying gait, pupil dilatation, tonic convulsive seizures, coma | 65, 196 |
| Fox | Stiffness of gait, spastic paralysis, abnormal sensitivity to pain, convulsions | 35, 63, 96–98 |
| Monkey | Ptosis, ataxia, lack of coordination, occasional convulsive seizures | 287 |
| Mouse | Tremor, occasional convulsions, spasticity of legs, backward jerking of the head, inability to walk | 300 |
| Rat | Incoordination of movements, swaying gait, head retraction, changes in muscular tonus, ataxia, disturbances of equilibrium, increased duration of rotational nystagmus | 39, 214 |
| Calf | Weakness, incoordination of legs, convulsions, head retraction | 122 |

tions of acute thiamine deficiency. The lesions produced in central neural structures by thiamine deficiency are summarized in table 2. In thiamine-deficient monkeys (219), no clinical or histological evidence of peripheral neuropathy or of degeneration of fibers in the spinal cord was observed. The authors conclude that the pathological picture is very similar to Wernicke's disease in man. The main difference is the absence in the monkey of vascular changes, so important in Wernicke's disease.

As regards behavior, rats deprived of thiamine (101, 289) increased their running in a rotating wheel until their activity fell off dramatically with the onset of neuromuscular symptoms of thiamine deficiency, culminating in spastic paralysis. Studies on the impairment of the learning capacity in rats deficient in B complex vitamins were summarized by Munn (186, p. 341).

THIAMINE DEFICIENCY IN MAN. Thiamine deficiency is recognized as the main etiological factor in the production of two clinical conditions with characteristic neurologic manifestations, beriberi and Wernicke's encephalopathy, which have been well described in medical literature (223, 242, 257, 291). Neurologically, beriberi is characterized by peripheral, ascending, symmetrical polyneuritis, with disturbances of both the afferent and the motor systems. Wernicke's encephalopathy is characterized by the clouding of consciousness and ophthalmoplegias, with polyneuritis and ataxia as less constant manifestations.

The effects of thiamine restriction in man have been studied experimentally by several research workers (125, 292). The effects of a prolonged partial restriction and a brief total deprivation of dietary thiamine were examined quantitatively in 10 young men, clinically normal at the start of the experiment (31). With other vitamins of the B complex made available in adequate amounts, the intake of 0.2 mg of thiamine per 1000 Cal. for 168 days was on the borderline of deficiency, as indicated by the level of urinary thiamine (37). In acute deprivation that followed, definite signs of deficiency developed in days or weeks, depending on the specific symptom. The first signs were anorexia and nausea. Severe deterioration observed on the 'psychoneurotic' scales ('Hypochondriasis,' 'Depression,' 'Hysteria') of the Minnesota Multiphasic Personality Inventory was subsequently reversed by thiamine supplements. On the other hand, changes in scores on the 'psychotic' scales ('Paranoia,' 'Schizophrenia,' 'Hypomania') were small.

Performance on standardized tests of intelligence was not affected adversely by thiamine deprivation. In the sensory area the most consistent change, with statistically significant decrement in deprivation and

TABLE 2. *Lesions of the Central Nervous System in Thiamine Deficiency*

| Location | Monkey | Fox | Rat | Pigeon |
|---|---|---|---|---|
| Cerebral cortex | + | + | − | − |
| Cerebellar cortex | +++ | +++ | − | × |
| Caudatum and putamen | ++++ | − | − | × |
| Pallidum | ++ | ++ | − | − |
| Thalamus | ++ | ++ | − | − |
| Substantia nigra | + | − | − | + |
| Hypothalamus | − | − | − | − |
| Superior colliculi | − | + | − | − |
| Inferior colliculi | +++ | +++ | − | − |
| Nuclei of cranial nerves | | | | |
| Third | +++ | +++ | − | × |
| Fourth | − | + | − | × |
| Sixth | +++ | − | ++ | − |
| Eighth | ++ | +++ | ++++ | ++ |
| Tenth | +++ | +++ | − | − |
| Nucleus gracilis and cuneatus | − | +++ | − | − |

× = lesion present, no degree indicated.

TABLE 3. *Neurologic Manifestations of Riboflavin Deficiency in Animals*

| Animal | Manifestations | References |
|---|---|---|
| Chicken | Degeneration of myelin sheaths in peripheral nerves, 'curled toes' paralysis | 210 |
| Dog | Ataxia, weakness, loss of deep reflexes, coma, demyelination in dorsal columns of spinal cord and peripheral nerves | 9, 237, 264 |
| Monkey | Incoordination, faulty grasping reflex, diminished strength of limbs | 286 |
| Mouse | Myelin degeneration in brachial and sciatic nerves, and in dorsal columns of the spinal cord | 147 |
| Pig | Myelin degeneration of sciatic and brachial nerves, collapse | 204, 294 |
| Rat | Paralysis, degeneration of myelin sheaths and lesions in axis cylinders of sciatic nerve | 64, 239 |

return toward 'normal' upon supplementation, was observed in the pressure-pain threshold measured by means of a sphygmomanometer cuff applied to the calf. Manual speed (involving large movements of the arm and requiring some skill), complex body-reaction times to visual stimuli, and toe-reaction times exhibited a similar pattern of statistically significant impairments.

### *Riboflavin*

Riboflavin participates in an important group of respiratory enzymes, the flavoproteins. The riboflavin content of the various parts of the brain is proportional to their respiration rate (139).

NEUROLOGICAL MANIFESTATIONS OF RIBOFLAVIN DEFICIENCY IN ANIMALS. Impairment of nervous function in riboflavin deprivation has been reported in several animal species. The main findings consist of low physical activity, collapse and coma. Anatomical lesions characterized by degeneration of peripheral nerves and the spinal cord have been reported. A summary of the neurologic findings in experimental riboflavin deficiency in animals is given in table 3.

Administration of riboflavin analogues has been used as a tool for the production of riboflavin deficiency (299), resulting in 'hyperirritability.' Other components of the diet appear to be important in the production of the neural manifestations of riboflavin deficiency. A high-fat diet favors the development of neurologic symptoms in the rat (64, 239).

The specificity of the neural manifestations of riboflavin deficiency is still a controversial matter. Patek *et al.* (204) suggested that the spastic paralysis observed in their riboflavin-deficient pigs may be due to other concomitant vitamin deficiencies and not to the lack of riboflavin itself. Follis (77, p. 163) considers the pathological alterations (myelin degeneration of some peripheral nerves and of the dorsal columns of the spinal cord) as 'equivocal.'

RIBOFLAVIN DEFICIENCY AND THE NERVOUS SYSTEM IN MAN. In 1938 Sebrell & Butler (235, 236) described the clinical picture of riboflavin deficiency in man. Some of the skin lesions were already known to be present in certain clinical conditions characterized by neurologic symptoms (259, 260). Stannus (261) believed that the neurologic manifestations were the consequence of capillary dysergia. The alteration in nervous function would then be due, not directly to a chemical lesion localized in the nervous cell itself, but to a primary lesion of the capillaries. Recent work on experimental riboflavin deficiency in man has given little indication of impairment of nervous functions (110, 111).

Work done in this laboratory (134) showed that normal young men suffer no neurophysiological handicap from subsistence for at least 5 mo. on a diet providing 0.31 mg of riboflavin per 1000 Cal. which represents one fifth of the recommended daily allowance (79).

### *Nicotinic Acid (Niacin)*

The physiological role of nicotinic acid depends on its participation in the molecule of three important coenzymes, the diphosphopyridine and triphosphopyridine nucleotides (or coenzymes I and II) and the more recently discovered coenzyme III. These coenzymes act as hydrogen acceptors in the dehydrogenation of numerous metabolically important substances.

Only two mammalian species, dog and man, develop characteristic niacin deficiency states (115) which can be easily differentiated from other nutritional deficiencies. In man it is generally identified with the syndrome of pellagra, although pellagra represents a complex nutritional deficiency involving nicotinic acid, tryptophan and perhaps factors antagonistic to nicotinic acid. Experience during the Spanish Civil War and World War II made it clear that most

if not all the neurologic disorders seen in clinical pellagra are due to other deficiencies. The mental disturbances, however, seem to be more directly related to the deficiency of nicotinic acid and, therefore, form a true part of the picture of 'pellagra' in so far as this disease is considered as caused by a deficiency of nicotinic acid.

Pellagra has been produced experimentally in man in the classic work of Goldberger (89). More recently, Goldsmith and her associates (90) produced perhaps the purest form of nicotinic acid deficiency. No neurologic disturbances were described, but some mental alterations consisting of apathy and depression were noted. The specificity of these mental alterations as manifestations of nicotinic acid deficiency is supported by the therapeutic effects of this vitamin. Administration of nicotinic acid to pellagra patients produces striking changes in mental condition, while no improvement or even worsening of the neurologic manifestations may take place (93, 95; 257, p. 44). These mental disturbances reappear when the drug is stopped (256).

The mental manifestations of pellagra begin in most of the cases very early and may be mistaken for symptoms of a psychoneurosis. The patients complain of depression, insomnia, feeling of fatigue, fears, anxiety, emotional instability and impairment of memory. Psychosensory disturbances are present in advanced stages of the disease. Mania, hallucinations and delirium may develop.

In a careful study of the mental disturbances of pellagra (151), the psychotic manifestations were traced to the organic sensory disturbances which frequently accompany the disease. The clouding of consciousness facilitates the translation of perverted sensibility into hallucinations. The burning sensations, which so often appear in conjunction with pellagra, probably lead pellagrins on occasion to drown themselves according to the classic pellagrologists.

The role of niacin, with special reference to the psychiatric manifestations of pellagra, was reviewed recently by Gregory (100). Mental signs, 'psychoneurotic' in character, of mild niacin deficiency, labeled as 'pellagra sine pellagra,' may occur in the absence of the typical lesions of the skin, mucous membranes and gastrointestinal system.

Closely related is the syndrome termed 'nicotinic acid deficiency encephalopathy' (124), considered by some authors as an acute form of nicotinic acid deficiency in contrast to the more chronic form of pellagra. The syndrome (40, 269) consists of clouding of consciousness, cogwheel rigidity, and uncontrollable grasping and sucking reflexes.

TABLE 4. *Neurologic Manifestations of Panthothenic Acid Deficiency in Animals*

| Animal | Symptoms and Lesions | References |
|---|---|---|
| Chicken | Myelin and axon degeneration in lateral and anterior spinal cord columns | 211, 240 |
| Dog | Irritability, spasticity of hind quarters, convulsions, coma | 229 |
| Monkey | Ataxia | 159 |
| Mouse | Hyperirritability, 'pain,' convulsions, paralysis of hind legs, spasticity of extremities, subnormal gait, myelin degeneration of spinal cord, posterior roots and sciatic nerve | 126, 183, 298 |
| Pig | Incoordination of movements in hind legs, spastic gait (goose stepping), chromatolysis of cells in dorsal root ganglia | 78, 112, 238, 267 |

*Pantothenic Acid*

This vitamin is a constituent of coenzyme *A* which participates in a fundamental way in the intermediary metabolism of carbohydrate and fat (191), and in the synthesis of acetylcholine. Deficiency of pantothenic acid has been produced experimentally in different animal species (table 4) and, more recently, in man. The pig appears to develop the most typical manifestations, including the spastic gait described as 'goose stepping.' The nervous manifestations appear generally in late stages of the deficiency, and for this reason some authors consider them as secondary changes.

A relationship of pantothenic acid to nervous function in man has been suspected since 1946 when Gopalan (91) reported successful results of the treatment of the 'burning feet' syndrome with this vitamin. Bean and his associates (11, 12) demonstrated that normal young men subsisting on a diet deficient in pantothenic acid or given a pantothenic acid antagonist (omega-methyl-pantothenic acid) develop a clinical picture in which altered nervous function is clearly manifest. The main signs are torpor, apathy and depression, and a neuromotor disorder with paresthesias and burning sensations. Although there are differences between the typical 'burning feet' and the syndrome produced experimentally by Bean *et al.*, there is no doubt that some of the basic neurologic disturbances of the 'burning feet' syndrome are reproduced in experimental pantothenic acid deficiency.

*Vitamin $B_6$ (Pyridoxine)*

In spite of the fact that vitamin $B_6$ was identified 20 years ago (20), its participation in biochemical reactions taking place in the nervous system has been made clear only in the last few years. The most important function of vitamin $B_6$ is related to the role of pyridoxal phosphate in the metabolism of amino acids and proteins (273) and, more specifically, in the reactions of transamination and decarboxylation (cf. 276).

It is likely that in pyridoxine deficiency the original defect consists of some alteration in the ability of the nerve cell to handle the amino acids, particularly the glutamic acid and its amide, but there is no definite evidence regarding the biochemical changes ultimately responsible for the alterations in excitability of the brain.

MANIFESTATIONS OF DEFICIENCY IN ANIMALS. The neurologic manifestations are among the most characteristic and constant signs of pyridoxine deficiency in animals. Typical convulsive seizures can be produced in rats (38). The fits resemble typical human epilepsy and appear in the rat after some 20 wk. of maintenance on the deficient diet. Similar seizures have been obtained by the administration of antagonists of pyridoxine (desoxypyridoxine, isonicotinic acid hydrazide, and semicarbazide). The neurologic signs in vitamin $B_6$ deficiency are summarized in table 5.

Other neurological symptoms are not so characteristic as the convulsive seizures and consist mainly of incoordination of movements, spastic gait and paralysis. The convulsive seizures are related to an increase of the irritability of the brain (46). The electroshock threshold of pyridoxine-deficient rats is rapidly elevated by administration of pyridoxine.

MANIFESTATIONS OF DEFICIENCY IN MAN. The production of convulsive seizures in man by deficiency of vitamin $B_6$ was first reported by Snyderman *et al.* (254, 255) in a defective infant fed a synthetic diet. The convulsions were promptly corrected by the intravenous administration of pyridoxine chlorhydrate. Convulsive seizures were observed by various authors in infants fed commercial formulas (41, 158, 176). Hunt *et al.* (116) reported a case of recurrent convulsive seizures controlled by the administration of pyridoxine. Livingston *et al.* (150) observed no improvement in cases of epilepsy of various types.

Neurological manifestations of pyridoxine deficiency have been induced repeatedly by giving pyridoxine antagonists. Deficiency symptoms, including polyneuritis, were produced by administration of desoxypyridoxine and controlled by pyridoxine treatment (278). Convulsive seizures produced in man and animals (217) by administration of isoniazide respond to pyridoxine therapy. The central nervous system syndrome which accompanies vitamin $B_6$ deficiency in infancy is considered to include the following manifestations (42): hyperirritability, gastrointestinal distress, increased startle responses and convulsive seizures. Changes in the EEG, consisting of increased voltage and slow waves, were reported during seizures (41); but no abnormalities are found during the interseizure periods.

TABLE 5. *Neurologic Manifestations of Pyridoxine Deficiency in Animals*

| Animal | Manifestations | References |
|---|---|---|
| Chicken | Convulsions | 127, 142 |
| Duck | Convulsions, paralysis | 103 |
| Turkey | Convulsive seizures | 22 |
| Calf | Convulsions | 123 |
| Dog | Epileptiform convulsions, degeneration of myelin sheaths in peripheral nerves and spinal cord | 187, 263 |
| Hamster | Ataxic gait, paresis, priapism | 234 |
| Monkey | Hyperirritability, ataxia | 159, 220 |
| Mouse | Ataxia of hind legs | 25 |
| Pig | Ataxia, muscular incoordination, spastic gait, epileptiform fits, degeneration of peripheral nerves, later necrosis of cells in dorsal root ganglia | 78, 113, 140 |
| Rat | Epileptiform seizures | 38, 45, 143, 205 |

*Vitamin $B_{12}$ (Cyanocobalamine)*

This vitamin is concerned with the biosynthesis of the methyl groups but perhaps not with the process of transmethylation itself (272). It appears to be important also for the reduction of coenzyme A and, therefore, it may be involved in the intermediate metabolism of carbohydrate and fat. The importance of vitamin $B_{12}$ for the nervous system is demonstrated by the neurologic disturbances characteristic of pernicious anemia, fundamentally a deficiency of $B_{12}$ (17). Jewesbury (118) proposed to call the neurologic syndrome of pernicious anemia the 'vitamin $B_{12}$ deficiency neuropathy.'

Deficiency of this vitamin may cause important congenital defects and structural alterations of the nervous organs. Newborn rats from dams kept on a diet devoid of vitamin $B_{12}$ develop hydrocephalus

(108, 198, 199). A lack of myelinization was observed in chick embryos, with reduction of nucleic acid in the spinal cord, the spinal ganglia and the sympathetic ganglia (5, 69). The neurologic picture of pernicious anemia in man indicates alterations of both the posterior and lateral columns of the spinal cord (141, 146) with ataxic gait, positive Romberg signs, absence of knee and ankle jerks, presence of extensor plantar reflexes, absence of abdominal reflexes, tenderness of the calf muscles, and sensory loss. The pathological findings show degeneration of the white matter in the thoracic segments of the spinal cord, affecting first the myelin sheath and later the axis cylinder. Retrograde degeneration may be seen in the Betz cells of the motor cortex and in the cells of Clarke's column. Demyelinization of the peripheral nerves of the lower limbs has been observed as well as ocular disturbances (dimness of vision, diplopia, nystagmus and pupillary anomalies). Mental symptoms are seen (257, p. 110), with variable intensity and order of presentation. They vary from slight disorders of mood or mental slowness to maniacal episodes, confusion and progressive mental enfeeblement.

There is evidence that the neurologic and mental disturbances of pernicious anemia are not the consequence of the anemia itself, but rather a consequence of some metabolic disturbance in the nervous tissue caused by the vitamin deficiency. Scheinberg (230) observed a decrease both in the oxygen and the glucose consumption of the brain of pernicious anemia patients. Administration of $B_{12}$ produced an improvement of the mental disturbances and an increase of the oxygen consumption. More recent observations indicate that vitamin $B_{12}$ deficiency may be associated with an alteration of pyruvate metabolism (59).

The metabolic defect of the brain in pernicious anemia results in alterations of the electroencephalogram (227). With the improvement of the mental condition produced by the administration of vitamin $B_{12}$, there is also a tendency for the electroencephalographic rhythms to become normal. Walton *et al.* (290) have also found the EEG to be made normal by administration of vitamin $B_{12}$ in pernicious anemia patients.

### *Nutritional Neuropathies*

This term is applied to a variety of neurological syndromes associated with nutritional deficiencies. One such syndrome associated with malnutrition was observed in the course of the Spanish Civil War (94, 95). A list of the main clinical features is given in table 6. Thiamine, riboflavin and nicotinic acid were ineffective in its treatment, but good results were obtained with yeast, both fresh and autoclaved. The conclusion was drawn that the paresthetic-causalgic syndrome was a nosological entity different from pellagra but frequently associated with this disease, and that it was due to a deficiency of some thermostable factors or factors of the vitamin B complex. Later Gopalan (91) in India recorded therapeutic success with pantothenic acid in patients with similar symptoms. After World War II numerous reports dealt with related syndromes (44, 55, 88, 95, 249, 252, 257).

TABLE 6. *Neurologic and Other Clinical Features of Nutritional Neuropathy in Madrid**

| | | | |
|---|---|---|---|
| Paresthesias | 98 | Dysphagia | 21 |
| Causalgic symptoms | 53 | Menstrual disorders | 31 |
| Neurasthenia | 88 | Urgency of micturition | 39 |
| Visual disturbances | 42 | Polyuria | 33 |
| Sensations of coldness | 51 | Nycturia | 18 |
| Disturbances of gait | 58 | Diarrhea | 35 |
| Glossitis | 47 | Constipation | 16 |
| | | Pernio | 11 |

* Frequency of occurrence in 98 cases studied by Grande & Peraita (95).

From a physiological point of view this syndrome is of interest in that the nutritional deficiency responsible for its development appears to affect preferentially sensory functions and the autonomic system, in particular, the vasomotor innervation. There is a striking contrast between the neurologic manifestations of beriberi and those of the 'burning feet' syndrome (207).

### *Vitamin A*

There is no evidence of the involvement of vitamin A in neuronal metabolism or in the formation and maintenance of myelin (295). It is of interest in the present context on two accounts: *a*) the mechanical production of nervous lesions in vitamin A deficiency, resulting from disproportionate growth of the bony structures which surround the central nervous system; and *b*) the role of vitamin A in the function of the rods of the retina.

In a series of studies carried over a period of some 20 years, Mellanby (167) provided experimental evidence that in puppies vitamin A deficiency causes a general thickening and dysplasia of bone. The hypertrophy and the altered shape of bones result in widespread mechanical lesions, involving both the

peripheral and the central nervous system. The medulla oblongata, pons, cerebellum and cranial sensory nerves are especially liable to suffer severe damage. In young ducks a vitamin-A deficient diet produces buckling and twisting of the spinal cord, hemorrhages and necrosis of the gray and white matter, and degeneration of fiber tracts and nerve cells (75). Vitamin A deficiency produces an elevation of the pressure of the cerebrospinal fluid in dogs (165) and in calves (178). This effect, however, does not appear to be necessarily related to the osseous thickening, since in calves papilledema and high pressure decrease rapidly when vitamin A is given. It has been suggested that the phenomenon may be due to an alteration of the ependyma which is of epithelial origin and, like other epithelia, depends for normal function on an adequate supply of vitamin A.

Vitamin A participates in the resynthesis of rhodopsin (288). Accordingly, its deficiency impairs dark adaptation. Morgan (181) has shown, by means of a behavioral technique in which albino rats were required to choose between a lighted and a dark panel, that the brightness of the test patch at which the animals discriminated accurately after a given time spent in the dark was substantially higher in the vitamin-A deficient than in the control animals receiving a supplement of cod liver oil.

In man the increase in the light threshold of the dark-adapted eye was reported after distressingly variable lengths of vitamin deprivation (192). Careful studies made in Great Britain (114) indicate that vitamin A deficiency is much less readily induced in hitherto well-fed adults than has been previously supposed. A large rise in the rod threshold, determined after 20 min. of dark adaptation, was obtained only in 3 out of 16 subjects, at about 10, 12 and 20 mo., respectively, from the start of the experiment. Their cone-rod transition time was lengthened. This feature of vitamin A deficiency may occur at the same time as the deterioration of the rod threshold or may precede it. A fall of the average plasma level to below 50 IU per 100 ml (normal average, 120 IU) preceded the deterioration of dark adaptation by a few weeks.

Electrophysiologically, the functional capacity of the rods may be assessed on the basis of an electroretinogram. The electroretinographic tracing represents the action-potential response of the rods of the retina in a dark-adapted eye exposed to a flash of light. When the vitamin A content of the blood reaches a critically low level (about 20 IU per 100 ml of plasma) patients develop night blindness and the electroretinogram becomes suddenly extinguished or the b-wave becomes very small (56). This is a reversible phenomenon, representing a functional (biochemical) change rather than a structural lesion. The electroretinographic response returns to normal in the course of treatment with vitamin A.

### *Vitamin E (Tocopherol)*

The relationship between vitamin E deficiency and certain alterations of the reproductive system, musculature and vascular system is well established, but its role in the metabolism of the nervous system is not clear (157). Histopathological changes in the nervous system of vitamin E deficient animals have been observed only in a limited number of species, and there is much disagreement as to the specificity of the lesions and their causal relationship to the deficiency of tocopherol. Lesions of the fibers of the dorsal columns and the dorsal roots are prominent (60, 148) and account for the ataxia observed in tocopherol-deficient rats. The lesions of the anterior horn neurons described by Einarson & Ringsted (61) were denied by other authors, and Malamud *et al.* (153) concluded that no constant lesions can be found either in the lower or upper motor neuron system. The pathological changes in the musculature do not appear to be correlated with neurological lesions, and it is generally accepted at present that the changes in skeletal musculature are myogenic.

In the chicken (202, 203), the syndrome of 'nutritional encephalomalacia' is characterized by motor incoordination and ataxia, spasticity of the legs, head retraction and opisthotonus, tremors, somnolence, stupor, and death. Pathological examination shows alterations especially in the cerebellum, which include changes in the fibers and cells, with degeneration of the Purkinje cells, and the small cells of the granular layer. It is doubtful whether these lesions are a direct consequence of the vitamin E deficiency. They may be a consequence of vasomotor disturbances (296).

Similar alterations were found in the spontaneous disease of chickens called 'crazy chick disease' which may be considered as a subacute avitaminosis E. This disease has a seasonal occurrence, with ischemic necrosis, extensive fibrosis of the cerebellum (128) and degeneration of the Purkinje cells (293). Tremors and incoordination were described in the vitamin-E deficient rat (152) and some changes in behavior were noted (16). The existence of changes in the central nervous system of rats deficient in vitamin E

has been denied by Olcott (197) and Pappenheimer (201). There is also disagreement as to the presence of alterations of the nerve endings in the muscles and in the central synapses (50, 271).

Very likely the degeneration of the posterior column and posterior roots fibers in the rat is directly related to the vitamin E deficiency, but there is no evidence that the other neuropathological findings in this condition can be attributed directly to the tocopherol deficiency. Especially confusing is the situation with respect to vitamin E and certain neurological disturbances in man. After initial reports of success in the treatment of amyotrophic lateral sclerosis and progressive muscular atrophy by administration of vitamin E, most of the authors deny effectiveness of this treatment (cf. 162, p. 729).

## NONDEFICITARY ABNORMALITIES OF NUTRITIONAL ORIGIN

So far we have been concerned with alterations in nervous function and behavior resulting from the lack or relative deficiency of certain nutrients. Abnormalities may be produced also by the presence of substances in the diet which *a*) are mistaken for harmless food but which are actually toxic (e.g. some mushrooms), *b*) are not inherently toxic but are made so by the processing of foods (e.g. agenized flour producing canine hysteria), *c*) represent normal foodstuffs not toxic unless eaten in large amounts under conditions of unbalanced diet (e.g. lathyrus peas and other leguminous seeds), or *d*) are not toxic to normal individuals but produce nervous disturbances in persons with specific metabolic faults (e.g. the amino acid phenylalanine in persons lacking enzymes necessary for its normal metabolism).

### *Mushroom Poisoning*

Ingestion of the fruit bodies of certain species of the mushroom genus *Amanita* (*A. muscaria*, *A. pantherina*), containing bufotenin as the active substance, produces hallucinations and its use as an intoxicant among some Siberian tribes has long been known. In Mexico the 'sacred fungus,' teonanacatl, identified as *Panaeolus campanulatus* var. *sphinctrinus*, has served for centuries a similar purpose (67); and recently fungi belonging to other genera were described as having hallucinogenic properties.

### *Canine Hysteria*

The term has been applied in Great Britain to a pathological condition in dogs characterized by striking nervous symptoms, including paroxysmal attacks of hyperexcitability, running and barking or howling, manifestations of faulty vision, and clonic convulsions. Urination and defecation occur frequently during the convulsions, along with secretion of mucous saliva. The animals seem at this time indifferent to injury. They may appear normal between attacks which are often precipitated by external stimuli, such as noise or light. In the United States, the disease has been called 'fright disease,' 'running fits,' 'enzootic hysteria' and 'hyperkinesia.' This nervous disturbance is definitely dietary in origin (8, 169, 180, 284), appearing in dogs fed a diet containing agenized flour (166, 168, 179), the 'toxic' substance in which was finally identified as methionine sulphoxamine (13, 14, 34, 218). This substance is a metabolic antagonist (102) which interferes with the enzyme systems synthesizing glutamine in the brain and with the glutamyl transferase (200). It also interferes with the formation of bound acetylcholine in the cerebral cortex (274). It is toxic to rabbits (215) and ferrets (33), but seems to possess little or no toxicity for some animal species (rat); and there is no evidence of untoward effects of the agene-treated flour on human nervous function (62).

The EEG tracings of dogs receiving a diet containing wheat gluten (189, 190) or wheat flour treated with nitrogen trichloride (245) showed alterations as early as 3 days after the beginning of the diet before any clinical abnormality was noticed. In view of the similarity between the electroencephalographic tracings obtained in these dogs and those in human epilepsy, the name 'canine epilepsy' was suggested. Cats seem to be more resistant to agenized flour than dogs. Monkeys, although not developing convulsions, show a syndrome characterized by tremor of the extremities and weakness of the hind limbs which develop within 5 days of maintenance on the experimental diet.

### *Lathyrism*

The name designates a form of epidemic spastic paraplegia which develops in man in association with excessive consumption of lathyrus peas (especially *L. sativus*, *L. cicera* and *L. clymenum*). The disease itself has been known since ancient times, and Hippocrates described the association of weakness of the

legs with high consumption of certain leguminous seeds. The association with the consumption of lathyrus was clearly established in Spain after the Civil War (119).

Lathyrism is seen predominately in young adult males. The prodromal period, which may be only one night, is characterized by symptoms of coldness of the feet, muscle pains and cramps. The patient notices increasing stiffness and weakness of the legs and becomes unable to walk. Spastic paraplegia and rigidity of the legs develop and voluntary movements disappear. Once this state develops there is usually very little or no change in the neurologic picture. Sensations are normal, extensor plantar reflexes are present, and abdominal reflexes may be lost. Tendon reflexes are normal in the arms and hyperactive in the legs. No other manifestations are observed. In other respects, the patients appear healthy, and are free of signs of malnutrition and without noticeable psychic change.

The pathology of the disease in man is not well known. The best descriptions are those by Stockmann (262) and by Filimonoff (71). The latter found degeneration of Goll's tract and the cerebellar pathway at the level of the cervical spinal cord, as well as lesions of the cortical Betz cells. The pathology seems to correspond to the clinical manifestations of spastic paraplegia.

A pathological condition, later termed 'odoratism' (279), was produced in the rat fed another variety of lathyrus seed, the common garden pea (*Lathyrus odoratus*) (85, 144). The study culminated in the isolation of beta-aminopropionitrile which, when administered to rats, produces the disease (265). This substance is not contained in the seeds of all lathyrus varieties. The disease produced by *L. odoratus* is clearly different from human lathyrism, the primary lesions in odoratism affecting not the nervous system but tissues of mesenchymal origin.

*Cicerism*

Another disorder produced by ingestion of leguminous seeds is 'cicerism.' Jiménez-Diaz & Vivanco (120, 121) found that rats fed cooked chick-peas (*Cicer arietinum*) or protein extracted from these peas display nervousness, irritability and continuous movement, followed by abnormal gait and hind-leg hyperextension. Rapid deterioration follows with gross incoordination of movements, loss of righting and convulsive fits. Death occurs in a few days. The disorder is prevented by administration of methionine (92, 280) but not vitamins A, D, $B_1$, $B_2$, $B_6$, nicotinic acid or pantothenic acid. Since the effect is not produced by eating of the whole fresh pea, a protective factor apparently is present which is destroyed by cooking.

*Phenylpyruvic Oligophrenia*

This rare form of mental deficiency is due not to a lack of any essential nutrient but to a faulty metabolism. Specifically, there is an enzyme blockage of the transformation of phenylalanine to tyrosine. Phenylalanine accumulates in the blood and cerebrospinal fluid and is partly broken down to phenylpyruvic as well as phenyllactic and phenylacetic acids which appear in abnormal amounts in the urine. Mental deficiency in phenylketonuria is considered to be due to 'intoxication' by phenylalanine or one of its metabolites. Several reports indicate that feeding diets low in phenylalanine (7, 18, 297) results in behavioral improvement, but the identity of the neurotoxic factor was not definitely established. Clearly, the special diets should be initiated at an early age in order to prevent irreversible damage to the central nervous system.

REFERENCES


1. Abramovič, G. B. and S. S. Mnuchin. *Opyt Sovetskoj Mediciny u Velikoj Otečestvennoj Vojne* 28: 117, 1951.
2. Addis, T., L. J. Poo and W. Lew. *J. Biol. Chem.* 115: 111, 1936.
3. Adolph, E. F. and associates. *Physiology of Man in the Desert.* New York: Interscience, 1947.
4. Alexander, L. *Am. J. Path.* 16: 61, 1940.
5. Alexander, W. F. *Internat. Ztschr. Vitaminforsch.* 26: 408, 1956.
6. Anderson, J. E. and A. H. Smith. *J. Comp. Psychol.* 6: 337, 1926.
7. Armstrong, M. D. and F. H. Tyler. *J. Clin. Invest.* 34: 565, 1955.
8. Arnold, A. and C. A. Elvehjem. *J. Am. Vet. M. A.* 95: 303, 1939.
9. Axelrod, A. E., M. A. Lipton and C. A. Elvehjem. *Am. J. Physiol.* 128: 703, 1940.
10. Barron, G. P., S. O. Brown and P. B. Pearson. *Proc. Soc. Exper. Biol. & Med.* 70: 220, 1949.
11. Bean, W. B. and R. E. Hodges. *Proc. Soc. Exper. Biol. & Med.* 86: 693, 1954.
12. Bean, W. B., R. E. Hodges and K. Daum. *J. Clin. Invest.* 34: 1073, 1955.

13. Bentley, H. R., E. E. McDermott, J. Pace, J. K. Whitehead and T. Moran. *Nature, London* 164: 438, 1949.
14. Bentley, H. R., E. E. McDermott and J. K. Whitehead. *Nature, London* 165: 735, 1950.
15. Berry, C., C. Neumann and J. C. Hinsey. *J. Neurophysiol.* 8: 315, 1945.
16. Bersot, H. *Schweiz. Arch. Neurol. u. Psychiat.* 49: 286, 1942
17. Bethell, F. H. In: *Vitamins. I*, edited by W. H. Sebrell and R. S. Harris. New York: Acad. Press, 1954, p. 491.
18. Bickel, H. *Exper. Med. & Surg.* 12: 114, 1954.
19. Biel, W. C. *Comp. Psychol. Monogr.* No. 74, 1938.
20. Birch, T. W. and P. György. *Biochem. J.* 30: 304, 1936.
21. Bird, F. H. *Poultry Sc.* 25: 396, 1946.
22. Bird, F. H., F. H. Kratzer, V. S. Asmudson and S. Lepkovsky. *Proc. Soc. Exper. Biol. & Med.* 52: 44, 1943.
23. Black, D. A. K., R. A. McCance and W. F. Young. *J. Physiol.* 102: 406, 1944.
24. Blaxter, K. L., J. A. F. Rook and A. M. Macdonald. *J. Comp. Path. & Therap.* 64: 157, 1954.
25. Boutwell, R. K., H. P. Rusch and R. Chiang. *Proc. Soc. Exper. Biol. & Med.* 77: 860, 1951.
26. Brooke, R. O. and A. H. Smith. *J. Biol. Chem.* 100: 105, 1933.
27. Brožek, J. In: *Methods for Evaluation of Nutritional Adequacy and Status*, edited by H. Spector, M. S. Peterson and T. E. Friedman. Washington, D. C.: Nat. Res. Council, 1954, p. 155.
28. Brožek, J. In: *Methods for Evaluation of Nutritional Adequacy and Status*, edited by H. Spector, M. S. Peterson and T. E. Friedman. Washington, D. C.: Nat. Res. Council, 1954, p. 204.
29. Brožek, J. *J. Am. Dietet. A.* 31: 703, 1955.
30. Brožek, J. *Am. J. Clin. Nutrition* 3: 101, 1955.
31. Brožek, J. *Am. J. Clin. Nutrition* 5: 109, 1957.
32. Brožek, J., S. Wells and A. Keys. *Am. Rev. Soviet Med.* 4: 70, 1946.
33. Butler, J. A. V. and G. L. Mills. *Nature, London* 163: 385, 1949.
34. Campbell, P. N., T. S. Work and E. Mellanby. *Biochem. J.* 48: 106, 1951.
35. Carlström, B. and G. Jonsson. *Skand. vet. tskr.* 28: 144, 1938.
36. Carothers, J. C. *The African Mind in Health and Disease: A Study in Ethnopsychiatry.* World Health Organization Monogr. Ser. No. 17, 1953.
37. Caster, W. O. *Am. J. Clin. Nutrition* 5: 119, 1957.
38. Chick, H., M. M. El Sadr and A. N. Worden. *Biochem. J.* 34: 595, 1940.
39. Church, C. F. *Am. J. Physiol.* 111: 660, 1935.
40. Cleckley, H. M., V. P. Sydenstricker and L. E. Geeslin. *J. A. M. A.* 112: 2107, 1939.
41. Coursin, D. B. *J. A. M. A.* 154: 406, 1954.
42. Coursin, D. B. *Am. J. Clin. Nutrition* 4: 354, 1956.
43. Critchley, M. *Shipwreck-Survivors.* London: Churchill, 1943.
44. Cruikshank, E. K. *Vitamins and Hormones* 10: 2, 1952.
45. Daniel, E. P., O. L. Kline and C. D. Tolle. *J. Nutrition* 23: 205, 1942.
46. Davenport, V. D. and H. W. Davenport. *J. Nutrition* 36: 263, 1948.
47. Davis, D. R. *Med. Research Council (Brit.) Spec. Rep. Ser.* No. 275: 147, 1951.
48. Day, P. L. and J. S. Dinning. *Am. J. Clin. Nutrition* 4: 386, 1956.
49. Debray, C., M. Zarakovitch, B. Ransom, J. Jacquemin, J. Robert and M. Siraga. *Semaine hôp. Paris* 22: 863, 1946.
50. de Castro, F., C. Jiménez-Diaz and F. Vivanco. *Rev. clin. españ.* 6: 311, 1942.
51. de Jong, S. *Arch. néerl. Physiol.* 21: 465, 1936.
52. del Castillo, J. and L. Engbaek. *J. Physiol.* 124: 370, 1954.
53. del Castillo, J. and B. Katz. *Progr. Biophys. & Biophys. Chem.* 6: 121, 1956.
54. del Castillo, J. and L. Stark. *J. Physiol.* 116: 507, 1952.
55. Denny-Brown, D. *Medicine* 26: 41, 1947.
56. Dhanda, R. P. *A. M. A. Arch. Ophth.* 54: 841, 1955.
57. Dill, D. B. *Life, Heat, and Altitude.* Cambridge: Harvard, 1938.
58. Duncan, C. W., C. F. Huefman and C. S. Robinson. *J. Biol. Chem.* 108: 35, 1935.
59. Earl, C. J., M. F. S. El Hawary, R. H. S. Thompson and G. R. Webster. *Lancet* 264: 115, 1953.
60. Einarson, L. *Acta psychiat. et neurol. scandinav.* Suppl. 78: 9, 1952.
61. Einarson, L. and A. Ringsted. *Effect of Chronic Vitamin E Deficiency on the Nervous System and the Skeletal Musculature in Adult Rats.* Copenhagen: Levin & Munksgaard, 1938.
62. Elithorn, A., D. M. Johnson and M. A. Crosskey. *Lancet* 256: 143, 1949.
63. Ender, F. and A. Helgebostad. *Skand. vet. tskr.* 29: 1232, 1939.
64. Engel, R. W. and P. H. Philips. *Proc. Soc. Exper. Biol. & Med.* 40: 597, 1939.
65. Everett, G. M. *Am. J. Physiol.* 141: 439, 1944.
66. Eijkman, C. *Arch. path. Anat.* 148: 523, 1897.
67. Fabing, H. D. *Scient. Month.* 83: 232, 1956.
68. Fatt, P. and B. Katz. *J. Physiol.* 117: 109, 1952.
69. Ferguson, T. M., J. R. Couch and W. F. Alexander. *Internat. Ztschr. Vitaminforsch.* 26: 410, 1956.
70. Ferraro, A. and L. Roizin. *J. Neuropath. & Exper. Neurol.* 6: 383, 1947.
71. Filimonoff, I. N. *Ztschr. ges. Neurol. Psychiat.* 105: 76, 1926.
72. Finger, F. W. *J. Comp. & Physiol. Psychol.* 44: 557, 1951.
73. Finger, F. W. and L. S. Reid. *J. Comp. & Physiol. Psychol.* 45: 368, 1952.
74. Fitzgerald, M. G. and P. Fourman. *Clin. Sc.* 15: 635, 1956.
75. Fletcher, D. E. and R. H. Rigdon. *A. M. A. Arch. Neurol. & Psychiat.* 61: 199, 1949.
76. Flink, E. B., F. L. Stutzman, A. R. Anderson, T. Konig and R. Fraser. *J. Lab. & Clin. Med.* 43: 169, 1954.
77. Follis, *R. H. The Pathology of Nutritional Diseases.* Springfield: Thomas, 1948.
78. Follis, R. H., Jr., and M. M. Wintrobe. *J. Exper. Med.* 81: 539, 1945.
79. Food and Nutrition Board, National Research Council. *Recommended Dietary Allowances: Revised 1953.* Washington, D. C.: Nat. Acad. Sc.–Nat. Research Council Publ. No. 302, 1953.
80. Frolov, J. P. *Arch. biol. nauk* 21: 159, 1922.
81. Ganit, W. H. *Fed. Proc.* 9: 46, 1950.

82. Gantt, W. H. *Am. J. Clin. Nutrition* 5: 121, 1957.
83. Gantt, W. H. and W. Fleishmann. *Am. J. Psychiat.* 104: 673, 1948.
84. Gavrilescu, N. and R. A. Peters. *Biochem. J.* 25: 1397, 1931.
85. Geiger, B. J., H. Steenbock and H. T. Parsons. *J. Nutrition* 6: 427, 1933.
86. Gerard, R. W. *A. Res. Nerv. & Ment. Dis., Proc.* 18: 316, 1937.
87. Gerard, R. W. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955, p. 458.
88. Glussman, M. *Am. J. Med.* 3: 211, 1947.
89. Goldberger, J. *A. M. A. Arch. Int. Med.* 25: 451, 1920.
90. Goldsmith, G. A., H. P. Sarrett, N. D. Register and J. Gibbens. *J. Clin. Invest.* 31: 533, 1952.
91. Gopalan, C. *Indian M. Gaz.* 81: 22, 1946.
92. Grande, F. *Exper. Med. & Surg.* 12: 297, 1954.
93. Grande, F. and F. Jiménez. *Rev. san. e hig. púb.* 15: 1, 1941.
94. Grande, F. and F. Jiménez. *Rev. clin. españ.* 5. 29, 1942.
95. Grande, F. and M. Peraita. *Avitaminosis y Sistema Nervioso.* Barcelona: Miguel Servet, 1941.
96. Green, R. G. *Minn. Wildlife Dis. Invest.* 2: 106, 1936.
97. Green, R. G., W. E. Carlson and C. A. Evans. *Science* 92: 154, 1940.
98. Green, R. G., W. E. Carlson and C. A. Evans. *J. Nutrition* 21: 243, 1941.
99. Greenberg, D. M. and E. V. Tufts. *Am. J. Physiol.* 121: 416, 1938.
100. Gregory, I. *J. Ment. Sc.* 101: 85, 1955.
101. Guerrant, N. B. and R. A. Dutcher. *J. Nutrition* 20: 589, 1940.
102. Heathcote, J. G. and J. Page. *Nature, London* 166: 353, 1950.
103. Hegsted, D. M. and M. N. Rao. *J. Nutrition* 30: 367, 1945.
104. Helweg-Larsen, P., H. Hoffmeyer, J. Kieler, E. H. Thaysen, J. H. Thaysen, P. Thygesen and M. H. Wulff. *Acta med. scandinav.* Suppl. 274, 1952.
105. Henschel, A., H. L. Taylor and A. Keys. *J. Appl. Physiol.* 6: 624, 1954.
106. Himwich, H. E. *Brain Metabolism and Cerebral Disorders.* Baltimore: Williams & Wilkins, 1951.
107. Hoff, H. E., P. K. Smith and A. W. Winkler. *Am. J. Physiol.* 130: 292, 1940.
108. Hogan, A. G., B. L. O'Dell and J. R. Whitley. *Proc. Soc. Exper. Biol. & Med.* 74: 293, 1950.
109. Hoobler, S. W., H. D. Kruse and E. V. McCollum. *Am. J. Hyg.* 25: 86, 1937.
110. Horwitt, M. K. In: *Vitamins. III*, edited by W. H. Sebrell and R. S. Harris. New York: Acad. Press, 1954, p. 387.
111. Horwitt, M. K., O. W. Hills, C. C. Harvey, E. Liebert and D. L. Steinberg. *J. Nutrition* 39: 357, 1949.
112. Hughes, E. H. *J. Agr. Research* 64: 185, 1942.
113. Hughes, E. H. and R. L. Squibb. *J. Animal Sc.* 1: 320, 1942.
114. Hume, E. M. and H. A. Krebs. *Med. Research Council (Brit.) Spec. Rep. Ser.* No. 264, 1949.
115. Hundley, J. M. In: *Vitamins. II*, edited by W. H. Sebrell and R. S. Harris. New York: Acad. Press, 1954, p. 551.
116. Hunt, A. D., J. Stokes, W. W. McCrory and H. H. Stroud. *Pediatrics* 13: 140, 1954.
117. Hutter, O. F. and K. Kostial. *J. Physiol.* 124: 234, 1954.
118. Jewesbury, E. C. O. *Lancet* 267: 307, 1954.
119. Jiménez-Diaz, C. (editor). *Estudios de Nutrición.* Madrid: Dirección General de Sanidad, 1943.
120. Jiménez-Diaz, C. and F. Vivanco. *Rev. clin. españ.* 5: 263, 1942.
121. Jiménez-Diaz, C. and F. Vivanco. *Rev. clin. españ.* 33: 393, 1949.
122. Johnson, B. C., T. S. Hamilton, W. B. Nevens and L. E. Boley. *J. Nutrition* 35: 137, 1948.
123. Johnson, B. C., J. A. Pinkos and K. A. Burke. *J. Nutrition* 40: 309, 1950.
124. Jolliffe, N., K. M. Bowman, L. A. Rosenblum and H. D. Fein. *J. A. M. A.* 114: 307, 1940.
125. Jolliffe, N., R. Goodhart, J. Gennis and J. K. Cline. *Am. J. M. Sc.* 198: 198, 1939.
126. Jones, J. H., C. Foster, F. Dorfman and G. L. Hunter. *J. Nutrition* 29: 127, 1945.
127. Jukes, T. H. *Proc. Soc. Exper. Biol. & Med.* 42: 180, 1939.
128. Jungherr, E. L. *Ann. New York Acad. Sc.* 52: 104, 1949.
129. Keith, T. B., R. C. Miller, W. T. S. Thorp and M. A. McCarty. *J. Animal Sc.* 1: 120, 1942.
130. Kety, S. S., B. D Polis, C. S. Nadler and C. F. Schmidt. *J. Clin. Invest.* 27: 500, 1948.
131. Keynes, R. D. and P. R. Lewis. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955, p. 440.
132. Keys, A. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 515.
133. Keys, A., J. Brožek, A. Henschel, O. Mickelsen and H. L. Taylor. *The Biology of Human Starvation.* Minneapolis: Univ. Minnesota Press, 1950.
134. Keys, A., A. F. Henschel, O. Mickelsen, J. M. Brožek and J. H. Crawford. *J. Nutrition* 27: 165, 1944.
135. Korkes, S., A. del Campillo, S. K. Korey, J. R. Stern, D. Nachmanson and S. Ochoa. *J. Biol. Chem.* 198: 215, 1952.
136. Kruse, H. D., E. R. Orent and E. V. McCollum. *J. Biol. Chem.* 96: 519, 1932.
137. Kruse, H. D., E. R. Orent and E. V. McCollum. *Am. J. Physiol.* 101: 454, 1932.
138. Langfeld, H. S. *Psychol. Monogr.* No. 71, 1914.
139. Leeman, H. and E. Pickler. *Klin. Wchschr.* 20: 37, 1941.
140. Lehrer, W. P., A. C. Wiese, P. R. Moore and M. E. Ensminger. *J. Animal Sc.* 10: 65, 1951.
141. Leichtestern, O. *Deutsche med. Wchnschr.* 10: 849, 1884.
142. Lepkovsky, S. and F. H. Kratzer. *J. Nutrition* 24: 515, 1942.
143. Lepkovsky, S., M. E. Krause and M. K. Dimick. *Science* 95: 331, 1942.
144. Lewis, H. B., R. S. Fajans, M. B. Esterer, C. W. Shen and M. Olifant. *J. Nutrition* 36: 537, 1948.
145. Leyton, G. B. *Lancet* 251: 73, 1946.
146. Lichtheim, L. *Neurol. Zentrabl.* 6: 235, 1887.
147. Lippincott, S. W. and H. P. Morris. *J. Nat. Cancer Inst.* 2: 601, 1942.
148. Lipschutz, M. D. *Rev. neurol.* 62: 221, 1936.
149. Liu, C. N. and W. F. Windle. *A. M. A. Arch. Neurol. & Psychiat.* 63: 918, 1950.

150. Livingston, S., J. M. Hsu and D. C. Petersen. *Pediatrics* 16: 250, 1955.
151. Llopis, B. *Actas españ. neurol. y psiquiat.* 1: 174, 1940.
152. Mackenzie, C. G., J. B. Mackenzie and E. V. McCollum. *Proc. Soc. Exper. Biol. & Med.* 44: 95, 1940.
153. Malamud, N., M. M. Nelson and H. M. Evans. *Ann. New York Acad. Sc.* 52: 135, 1949.
154. Mannell, W. A. and R. J. Rossiter. *Brit. J. Nutrition* 8: 56, 1954.
155. Marriott, H. L. *Water and Salt Depletion.* Springfield: Thomas, 1950.
156. Marston, H. R. *Physiol. Rev.* 32: 66, 1952.
157. Mason, K. E. *Vitamins. III,* edited by W. H. Sebrell and R. S. Harris. New York: Acad. Press, 1954, p. 514.
158. May, C. D. *Pediatrics* 14: 269, 1954.
159. McCall, K. B., H. A. Waisman, C. A. Elvehjem and E. S. Jones. *J. Nutrition* 31: 685, 1946.
160. McCance, R. A., C. C. Ungley, J. W. L. Crossfill and E. M. Widdowson, *The Hazards to Men in Ships Lost at Sea, 1940–44.* Med. Research Council (Brit.) Spec. Rep. Ser. No. 291, 1956.
161. McDonald, I. W. *Australian Vet. J.* 22: 91, 1946.
162. McEachern, D. In: *Neurochemistry,* edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955, p. 715.
163. McGee, W. J. *Interstate Med. J.* 13: 279, 1906.
164. Meiklejohn, A. P. *New England J. Med.* 223: 265, 1940.
165. Mellanby, E. *J. Physiol.* 99: 467, 1941.
166. Mellanby, E. *Brit. M. J.* 2: 885, 1946.
167. Mellanby, E. *J. Physiol.* 105: 382, 1947.
168. Mellanby, E. *Brit. M. J.* 2: 288, 1947.
169. Melnick, D. and G. R. Cowgill. *J. Nutrition* 14: 401, 1937.
170. Meltzer, S. J. and J. Auer. *Am. J. Physiol.* 14: 366, 1905.
171. Meltzer, S. J. and J. Auer. *Am. J. Physiol.* 21: 400, 1908.
172. Miller, J. F. *Am. J. Dis. Child.* 67: 117, 1944.
173. Miller, L. L. *J. Biol. Chem.* 172: 113, 1948.
174. Miller, R. C., T. B. Keith, M. A. McCarty and W. T. S. Thorp. *Proc. Soc. Exper. Biol. & Med.* 45: 50, 1940.
175. Minz, B. *Role of Thiamine in Nervous Transmission.* Springfield: Thomas, 1955.
176. Moloney, C. J. and A. H. Parmelee. *J. A. M. A.* 154: 405, 1954.
177. Money, J. *A. M. A. Arch. Neurol. & Psychiat.* 76: 296, 1956.
178. Moore, L. A. and J. F. Sykes. *Am. J. Physiol.* 130: 684, 1940.
179. Moran, T. *Lancet* 253: 289, 1947.
180. Morgan, A. F. and M. Groody. *J. Am. Vet. M. A.* 105: 406, 1944.
181. Morgan, C. T. *J. genet. Psychol.* 60: 109, 1942.
182. Morgulis, S. *Fasting and Undernutrition.* New York: Dutton, 1923.
183. Morris, H. P. and S. W. Lippincott. *J. Nat. Cancer Inst.* 2: 29, 1941.
184. Mouriquand, G., V. Edel and R. Chighinzola. *Internat. Ztschr. Vitaminforsch.* 25: 443, 1955.
185. Mouriquand, G., A. Leulier and G. Morin. *Compt. rend. Soc. de biol.* 112: 485, 1933.
186. Munn, N. *Handbook of Psychological Research on the Rat.* Boston: Houghton, 1950.
187. Mushett, C. W., R. B. Stebbins and M. N. Barton. *Tr. New York Acad. Sc.* 9: 291, 1947.
188. Neuwerth, I. and G. B. Wallace. *J. Pharmacol.* 45: 109, 1932.
189. Newell, G. W., T. C. Erickson, W. E. Gilson and C. A. Elvehjem. *Proc. Soc. Exper. Biol. & Med.* 65: 115, 1947.
190. Newell, G. W., T. C. Erickson, W. E. Gilson, S. N. Gershoff and C. A. Elvehjem. *J. A. M. A.* 135: 760, 1947.
191. Novelli, G. D. *Physiol. Rev.* 33: 525, 1953.
192. *Nutrition Revs.* 7: 234, 1949.
193. *Nutrition Revs.* 9: 113, 1951.
194. *Nutrition Revs.* 11: 201, 1953.
195. Ochoa, S. and R. A. Peters. *Biochem. J.* 32: 1501, 1938.
196. Odom, G. and D. McEachern. *Proc. Soc. Exper. Biol. & Med.* 50: 28, 1942.
197. Olcott, H. S. *J. Nutrition* 15: 221, 1938.
198. Overholser, M. D., J. R. Whitley, B. L. O'Dell and A. G. Hogan. *Anat. Rec.* 109: 73, 1951.
199. Overholser, M. D., J. R. Whitley, B. L. O'Dell and A. G. Hogan. *Anat. Rec.* 120: 917, 1954.
200. Pace, J. and E. E. McDermott. *Nature, London* 169: 415, 1952.
201. Pappenheimer, A. M. *J. Mt. Sinai Hosp. New York* 7: 65, 1940.
202. Pappenheimer, A. M. *On Certain Aspects of Vitamin E Deficiency* (Am. Lect. Ser. 17). Springfield: Thomas, 1948.
203. Pappenheimer, A. M. and M. Goettsch. *J. Exper. Med.* 53: 11, 1931.
204. Patek, A. J., J. Post and J. Victor. *Am. J. Physiol.* 133: 47, 1941.
205. Patton, R. A., H. W. Karn and H. E. Longenecker. *J. Biol. Chem.* 152: 181, 1944.
206. Peck, C. H. and S. J. Meltzer. *J. A. M. A.* 67: 1131, 1916.
207. Peraita, M. *Internat. Ztschr. Vitaminforsch.* 24: 1, 1952.
208. Peters, R. A. *Lancet* 230: 1161, 1936.
209. Peters, R. A. *Brit. M. Bull.* 9: 116, 1953.
210. Phillips, P. H. and R. W. Engel. *J. Nutrition* 16: 451, 1938.
211. Phillips, P. H. and R. W. Engel. *J. Nutrition* 18: 227 1939.
212. Plaut, H. *Ztschr. Psychother.* 5: 168, 1955.
213. Plumlee, M. P., D. M. Thrasher, W. M. Beeson, F. N. Andrews and H. E. Parker. *J. Animal Sc.* 15: 352, 1956.
214. Pricket, C. O. *Am. J. Physiol.* 107: 459, 1934.
215. Radomski, J. L., G. Woodard and A. J. Lehman. *J. Nutrition* 36: 15, 1948.
216. Razdol'skij, I. Ja. *Opyt Sovetskoj Mediciny u Velikoj Otečestvennoj Vojne* 28: 113, 1951.
217. Reilly, R. H., K. F. Killam, E. H. Jenney, W. H. Marshall, T. Tausig, N. S. Apter and C. C. Pfeiffer. *J. A. M. A.* 152: 1317, 1953.
218. Reiner, L., F. Misani, T. W. Fair, P. Weiss and M. G. Cordasco. *J. Am. Chem. Soc.* 72: 2297, 1950.
219. Rinehart, J. F., M. Friedman and L. D. Greenberg. *A. M. A. Arch. Path.* 48: 129, 1949.
220. Rinehart, J. F. and L. D. Greenberg. *Am. J. Path.* 25: 481, 1949.
221. Rof, J. and F. Grande. *Rev. clin. españ.* 9: 387, 1943.

222. Rose, W. C. and S. H. Epstein. *J. Biol. Chem.* 127: 677, 1939.
223. Rossiter, R. J. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955, p. 696.
224. Rozental, I. S. *Arch. biol. nauk* 21: 151, 1922.
225. Ruch, F. L. *J. Comp. Psychol.* 14: 321, 1932.
226. Salem, H. M. *Biochem. J.* 57: 227, 1954.
227. Samson, D. C., S. N. Swisher, R. M. Christian and G. L. Engel. *A.M.A. Arch. Int. Med.* 90: 4, 1952.
228. Saphir, W. *J. A. M. A.* 129: 510, 1945.
229. Schaefer, A. E., J. M. McKibbin and C. A. Elvehjem. *J. Biol. Chem.* 143: 321, 1942.
230. Scheinberg, P. *Blood* 6: 213, 1951.
231. Schiele, B. C. and J. Brožek. *Psychosom. Med.* 10: 31, 1948.
232. Schlesinger, H. In: *Handbuch der Neurologie*, edited by O. Bumke and O. Foerster. Berlin: Springer, 1936, vol. 13, p. 1008.
233. Schüffner, W. In: *Ernährungslehre*, edited by W. Stepp. Berlin: Springer, 1939.
234. Schwartzman, G. and L. Strauss. *J. Nutrition* 38: 131, 1949.
235. Sebrell, W. H. and R. E. Butler. *Pub. Health Rep.* 53: 2282, 1938.
236. Sebrell, W. H. and R. E. Butler. *Pub. Health Rep.* 54: 2121, 1939.
237. Sebrell, W. H. and R. H. Onstott. *Pub. Health Rep.* 53: 83, 1938.
238. Sharma, G. L., R. L. Johnston, R. W. Luecke, J. A. Hoefer, M. L. Gray and F. Thorp. *Am. J. Vet. Res.* 13: 298, 1952.
239. Shaw, J. H. and P. H. Phillips. *J. Nutrition* 22: 345, 1941.
240. Shaw, J. H. and P. H. Phillips. *J. Nutrition* 29: 107, 1945.
241. Sihls, M. E. and E. V. McCollum. *J. Nutrition* 26: 1, 1943.
242. Shimazono, B. *Ergebn. inn. Med. u Kinderh.* 39: 1, 1931.
243. Shohl, A. T. *Mineral Metabolism*. New York: Reinhold, 1939.
244. Shohl, A. T. and S. B. Wolbach. *J. Nutrition* 11: 275, 1936.
245. Silver, M. L., R. E. Johnson, R. M. Kark, J. R. Klein, E. P. Monahan and S. S. Zevin. *J. A. M. A.* 135: 757, 1947.
246. Sinclair, H. M. *Brit. M. Bull.* 12: 18, 1956.
247. Sjollema, B. *Nutrition Abstr. & Rev.* 1: 621, 1932.
248. Sjollema, B. and L. Seekles. *Biochem. Ztschr.* 258: 471, 1933.
249. Smith, D. A. and M. F. A. Woodruff. *Deficiency Diseases in Japanese Prison Camps*. London: His Majesty's Stat. Off., 1951.
250. Smith, S. G. *Arch. Biochem.* 20: 473, 1949.
251. Smith, S. G. and T. E. Lasater. *Am. J. Physiol.* 164: 702, 1951.
252. Smitskamp, H. *A Neurovascular Syndrome Related to Vitamin Deficiency*. Amsterdam: Scheltema, 1947.
253. Snapper, I. In: *Clinical Nutrition*, edited by N. Jolliffe, F. F. Tisdall and P. R. Cannon. New York: Hoeber, 1950, p. 251.
254. Snyderman, S. E., R. Carretero and L. E. Holt. *Fed. Proc.* 9: 371, 1950.
255. Snyderman, S. E., L. E. Holt, R. Carretero and K. Jacobs. *J. Clin. Nutrition* 1: 200, 1953.
256. Spies, T. D., C. D. Aring, J. Gelperin and W. B. Bean. *Am. J. M. Sc.* 196: 461, 1938.
257. Spillane, J. D. *Nutritional Disorders of the Nervous System*. Baltimore: Williams & Wilkins, 1947.
258. Spillane, J. D. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955, p. 785.
259. Stannus, H. S. *Tr. Roy. Soc. Trop. Med. & Hyg.* 5: 112, 1912.
260. Stannus, H. S. *Tr. Roy. Soc. Trop. Med. & Hyg.* 7: 32, 1913.
261. Stannus, H. S. *Brit. M. J.* 2: 103, 140, 1944.
262. Stockman, R. *Edinburgh M. J.* 19: 277, 297, 1917.
263. Street, H. R., G. R. Cowgill and H. M. Zimmerman. *J. Nutrition* 21: 275, 1941.
264. Street, H. R., G. R. Cowgill and H. M. Zimmerman. *J. Nutrition* 22: 7, 1941.
265. Strong, F. M. *Nutrition Revs.* 14: 65, 1956.
266. Suzuki, M., T. Shamimura and S. Okade. *Biochem. Ztschr.* 43: 89, 1912.
267. Swank, R. L. and R. D. Adams. *J. Neuropath. & Exp. Neurol.* 7: 274, 1948.
268. Swank, R. L. and O. A. Bessey. *J. Nutrition* 22: 77, 1941.
269. Sydenstricker, V. P. and H. M. Cleckley. *Am. J. Psychiat.* 98: 83, 1941.
270. Taylor, H. L., A. Henschel, O. Mickelsen and A. Keys. *J. Appl. Physiol.* 6: 613, 1954.
271. Telford, I. R. *Anat. Rec.* 81: 171, 1941.
272. Thompson, R. H. S. and J. N. Cumings. In *Biochemical Disorders in Human Disease*, edited by R. H. S. Thompson and E. J. King. New York: Acad. Press, 1957, p. 401.
273. Tower, D. B. *Am. J. Clin. Nutrition* 4: 329, 1956.
274. Tower, D. B and K. A. C. Elliott. *J. Appl. Physiol.* 5: 375, 1953.
275. Trowell, H. C., J. N. P. Davies and R. F. A. Dean. *Kwashiorkor*. London: Arnold, 1954.
276. Umbreit, W. W. In: *Vitamins, II*, edited by W. H. Sebrell and R. S. Harris. New York: Acad. Press, 1954, p. 234.
277. Underwood, E. J. *Trace Elements in Human and Animal Nutrition*. New York: Acad. Press, 1956.
278. Vilter, R. W., J. F. Mueller, H. S. Glazer, T. Jarrold, J. Abraham, C. Thompson and V. R. Hawkins. *J. Lab. & Clin. Med.* 42: 335, 1953.
279. Vivanco, F. and C. Jiménez-Diaz. *Rev. clín. españ.* 40: 157, 1951.
280. Vivanco, F., C. Jiménez-Diaz and J. Palacios. *Rev. clín. españ.* 39: 168, 1950.
281. Vogt-Møller, P. *Biochem. J.* 25: 418, 1931.
282. von Muralt, A. *Vitamins and Hormones* 5: 93, 1947.
283. Waelsch, H. *Advances Protein Chem.* 6: 299, 1951.
284. Wagner, J. R. and C. A. Elvehjem. *J. Nutrition* 28: 431, 1944.
285. Wainio, W. W., B. Eichel, H. J. Eichel, P. Person, F. L. Estes and J. B. Allison. *J. Nutrition* 49: 465, 1953.
286. Waisman, H. A. *Proc. Soc. Exper. Biol. & Med.* 55: 69, 1944.
287. Waisman, H. A. and K. B. McCall. *Arch. Biochem.* 4: 265, 1944.
288. Wald, G. *Science* 113: 287, 1951.

289. Wald, G. and B. Jackson. *Proc. Nat. Acad. Sc., Washington* 30: 255, 1944.

290. Walton, J. N., L. G. Kiloh, J. W. Osselton and J. Farrall. *Electroencephalog. & Clin. Neurophysiol.* 6: 45, 1954.

291. Wernicke, C. *Lehrbuch der Gehirnkrankheiten für Aerzte und Studierende.* Kassel: Th. Fischer, 1881.

292. Wilder, R. M. In: *The Biology of Mental Health and Disease.* New York: Hoeber, 1952, p. 531.

293. Winter, H. *Australian Vet. J.* 32: 269, 1956.

294. Wintrobe, M. M., W. Buschke, R. H. Follis and S. Humphreys. *Bull. Johns Hopkins Hosp.* 75: 102, 1944.

295. Wolbach, S. B. and O. A. Bessey. *A. Res. Nerv. & Ment. Dis., Proc.* 22: 80, 1943.

296. Wolf, A. and A. M. Pappenheimer. *J. Exper. Med.* 54: 399, 1931.

297. Woolf, L. I., R. Griffiths and A. Moncrieff. *Brit. M. J.* 1: 57, 1955.

298. Woolley, D. W. *Proc. Soc. Exper. Biol. & Med.* 46: 565, 1941.

299. Woolley, D. W. *J. Biol. Chem.* 154: 31, 1944.

300. Woolley, D. W. and A. G. C. White. *J. Biol. Chem.* 149: 285, 1943.

301. Young, D. R. and H. Spector. *Am. J. Clin. Nutrition* 5: 129, 1957.

# Disturbances of neural function in the presence of congenital disorders[1]

SAMUEL P. HICKS | *Departments of Pathology, New England Deaconess Hospital, and Harvard Medical School, Boston, Massachusetts*

CHAPTER CONTENTS



ABNORMALITIES OF THE NERVOUS SYSTEM that result from faulty development are legion. They affect every kind of organism that has a nervous system and disturb function through the most devious mechanisms. Neurophysiologically speaking they have nothing in common except that they involve a nervous system. They may become manifest throughout the life of the organism, for development is something that goes on until death.

Two problems arise immediately in any consideration of congenital anomalies. One is how to draw a line between what is abnormal and what is biologic variation. Most of us agree on what are frank abnormalities but minor deviations are usually classified arbitrarily. A more difficult problem is how to decide when an abnormality is primarily a part of the abnormal developmental process and when it is a secondary consequence. Anencephaly and phenylketonuria are ordinarily considered to be developmental abnormalities, one expressed at an anatomic, the other at a biochemical level. However, the bruised brain that results when a chronic alcoholic drives his automobile into a tree may be viewed as a secondary consequence of the man's primary developmental disorder of personality, whatever its origin. In diabetes mellitus, which is a congenital inborn error of metabolism, retinopathy and neuropathy are usually thought of as intrinsic parts of the disease. However, would we all agree that cerebral arteriosclerotic apoplexy or hypoglycemic brain damage from therapeutic insulin are secondary to the diabetes, or are they, too, a primary part of the diabetic process? This sort of difficulty of distinguishing between primary and secondary processes is even more marked in the analysis of the disturbed neurophysiology of certain behavior disorders (2, 5, 21, 26).

It is obvious that some practical limit will have to be put on what is to be presented in this essay. Perhaps this can be done by considering several conditions involving vertebrates that most of us would agree are developmental in the primary sense, that is closely related to the genetic and epigenetic processes. At the same time by a choice of examples the extraordinary diversity of congenital neurologic disorders can be emphasized.

An understanding of how function is disturbed in these conditions rests on a grasp of how they develop. Therefore a review of certain aspects of neurogenesis and some ways it can go wrong is necessary before we can consider them. The primary determinants of how the organism will develop and be shaped by its environment, normally or abnormally, are the chromosomes in the egg, and they are present from the beginning. In this sense any deviation from normal develop-

[1] This work was supported by Public Health Service Grant B-382, United Cerebral Palsy and Atomic Energy Commission Contracts AT(30-1)1454 and 901.

ment pathways is quite literally 'congenital,' or 'present from the beginning.'[2] Chromosomes are in part composed of chains of segmented nucleotides and it is hypothesized that these act as templates for forming cellular proteins and that their molecular configurations provide a highly refined 'code' for determining all that is implied by genetic specificity (11, 16). Precisely how this intricate process of early protein production and the interactions of chemical processes ultimately leads to the formation of an alligator, a chicken, a phenylketonuric idiot or a normal man is only beginning to be understood. The codes normal for a given species can be and are constantly changed or 'mutated', the mutation in the chromosome may be thought of as leading to mutated proteins which in turn lead to biological variation or frank abnormality in development, depending on the degree of deviation. That segments of chromosomes, large and small, are ultimately responsible for recognizable characteristics or groups of characteristics in the adult organism is unquestioned, but there is no way of projecting 'straight lines' from genes to organs or to discrete functional units. There is not a gene for the brain, another for an arm, etc. Rather, seemingly unrelated structures may depend on the integrity of what seems to be a single genetic process. Some groups of structures may possibly depend on a constellation of genes in several chromosomes, a defect in any one of the different parts of the constellation leading to the same or a closely related abnormality. The hereditary ataxias, with their involvement of certain parts of the neuromuscular apparatus, may represent such a process.

Most spontaneous abnormalities arise from primary mutations or as a result of interference from the environment with genetically determined pathways of development. Abnormalities may express themselves at gross structural, biochemical or functional levels. When an environmentally triggered abnormality imitates a mutant, it is called a phenocopy. Some mutations are not expressed without the help of an environmental factor so that the distinction between the effects of mutations and phenocopies may not always be sharp. A third class of abnormalities, essentially anatomic, may result from frank destructive injury to the embryo (19, 24). They are not phenocopies in the sense above but rather reflect what happens to any 'normal' vertebrate when parts of it are destroyed during ontogeny. It might be said that such injuries bring out responses that reflect more the genetic similarities of developmental processes common to vertebrates than subtle mutant differences between individuals. Contrary to some popular medical and lay opinions, few instances of this class of anomalies are known outside of the laboratory. A well-known experimental example is damage to the prechordal mesoderm of embryos of amphibia, birds and mammals which results in degrees of head and brain anomalies, depending on how the experimenter inflicts the damage. Perinatal asphyxia in man and mammals, mechanical injuries (experimental and otherwise), and ionizing radiation may produce this class of abnormalities too by destroying certain tissues in the embryo.

In the evolution of the vertebrate nervous system, which seems to have been the superimposition of increasingly complex associative devices on a simple receptor-effector axis (18), the patterns of early ontogenesis have remained rather similar among the many present forms. Cleavage and formation of a blastula lead to a situation where an ectodermal layer or epiblast comes to overlie mesodermal cells and the latter induces the former to become a neural plate (34). This early plate can be shown by experiment to possess potentialities for an anterior brain or archencephalon and a posterior part or brain stem and spinal cord. These potentialities are scarcely evident before a much more extensive mosaic of future regions of the nervous system can be anticipated in the plate and its adjacent neural crest. As the plate rolls up into a tube, a pattern of successive series of proliferation centers appears in the mitotic cell layer of the tube and from these the whole central nervous system evolves. These early patterns are remarkably similar amongst the vertebrates as a whole (8). Each center gives rise to one or several bursts of proliferation and resulting cells migrate out appropriately to form layers of the pallium, the nuclei of the interbrain, the brain stem and the spinal cord. The processes of the neurons form the fiber systems and nerves.

Very early in embryonic life a sequence of self-determining processes becomes evident in the functional organization of the nervous system that leads to a specificity that almost makes each nerve cell in the body different from every other. Although one can interchange parts of the early embryonic neuraxis and the exchanged parts will rearrange their potentialities so that a nearly normal animal develops, this faculty for structural readjustment is lost as differentiation proceeds. When a motor nerve first grows into its muscle it takes on a specificity, apparently at the molecular level, that identifies it with

[2] 'Congenital disorder' in this chapter will mean developmental disorder.

that muscle and this enables it to make connections with central coordination centers appropriate for the function of that muscle only. That this really happens is demonstrated by experimentally making a nerve developing from the trunk, for example, grow into a forelimb. The nerve acquires the 'sign' of the limb muscles which somehow enables it to make connections with the coordination centers for the limb rather than the trunk from which it began. Each fiber from the retina becomes specific for the particular geographical part of the eye in which it originates, and sensory nerve fibers growing into the skin acquire a property that identifies them with a particular zone of the skin and no other. In the adult the specific quality of the nerve fibers has become incorrigible. In man this is well exemplified by the failure of a hypoglossal nerve, anastomosed to the distal part of a cut facial nerve, ever to take over the functions of a facial nerve. Numerous other examples of this self-determination process during the development of the nervous system involving the motor, sensory and special sense circuits may be found in Weiss (35, 36), Sperry (29, 30) and Stone (31). Altogether development is an inexorable business that follows along lines determined by the genetic endowment of the organism. The nervous system, to be sure, is an adaptive and adjusting mechanism (23), but the machinery for the mechanism is laid down in a manner predetermined by the ontogenetic processes.

With this brief reference to neural development we can pass on to descriptions of representative abnormalities. They will be grouped rather arbitrarily, for the separation of anatomic from biochemical disorders and late from early disturbances is often artificial. In each group, reference will be made to a number of examples (when there are a number) and one or two will then be considered in more detail.

## ANATOMIC ABNORMALITIES

Structural abnormalities of the nervous system that can be seen grossly or microscopically are innumerable in man (7) and in some other mammals (17). While the majority represent mutants and phenocopies in the sense outlined earlier, certain forms of trauma and asphyxia in the perinatal period in man can produce serious anatomic injuries that do not fall into the 'genetic' categories. The disturbances of function that go with this variety of anatomic disorders are as diverse as the structural patterns of damage that may result. Since the factors concerned—the kind of trauma, the asphyxia, hemorrhage and ischemia—are so variable and often combined, there is no specific pattern of injury. Of the patterns of grossly evident malformation that have their origin earlier in development than the perinatal period there are myriads. Diminutions in the gross size and convolutions of the cortex (microcephalies), and structural defects of the basal ganglia, corpus callosum, parts of the cerebellum and the brain stem are examples of the broad categories that can be seen. In general the disturbed function is directly referable to the defects. A relative lack of the lateral thoracolumbar (sympathetic) spinal cord gray columns or a discrepancy in the number of myenteric neural plexuses in the colon itself may lead to a pathologically distended colon (megacolon). Abnormalities of the cytoarchitecture of the cerebral cortex, basal ganglia and brain-stem nuclei at the microscopic level are numerous in variety and may be associated with degrees of mental retardation, behavior disorders or motor abnormalities.

A considerable number of developmental abnormalities express themselves in young adult life or even in old age. They too appear as structural abnormalities but they also illustrate how hard it is to categorize them as 'anatomic,' 'biochemical,' etc. Some will be mentioned in another section.

### *Anencephaly*

This is a not uncommon abnormality in man that illustrates anatomic deformity in just about its most severe form. It has been known at least since early Egyptian times (27), for the mummy of such an infant was found in a tomb for sacred animals. It was apparently believed by the Egyptians that the sire of the child must have been a monkey. The condition is characterized by severe gross deficit of the brain and upper spinal cord ranging from what is described as complete absence of brain to an open plate of neural tissue capable of some functional activity. Usually two bulging froglike eyes are present, cyclopia being a rare accompaniment. Most such infants or fetuses are females and the most likely background for the condition is that it represents a homozygous recessive genetic situation with variable expression. One judges that the deviation from normal developmental paths must first become evident at the time that the mesoderm is first inducing the nervous system, although by analogy with monsters in other animals it is puzzling why the eyes should be so well-developed. Possibly the involve-

ment of the eyes in the severe head defects seen in some experimental animal malformations simply reflects a slight difference in developmental patterns between man and other vertebrates involving the prechordal mesoderm.

Ballantyne (4) collected information about a considerable number of these monsters. Although they often go to term, they usually die soon after birth. Some survive for hours or, rarely, weeks. They live *in utero*, obviously, and move there. Respiratory, sucking and successful swallowing movements have been described, and some have passed urine and feces. It is remarkable how little nervous parenchyma seems to be necessary for some of the basic movements mentioned above to be carried out even though, from the descriptions given, they are rather crude and not always successful (as respiration or swallowing movements). On the other hand, in one case, a male cited by Ballantyne (4), there was no trace of cerebral hemispheres or cerebellum, the midbrain, medulla and pons were incomplete, but the cord was apparently normal. The infant lived 39 hr., his rectal temperature was 95°F, respirations were of the Cheyne-Stokes type at a rate of 9 per min., and his pulse rate was 138 per min. but intermittent during inspiration. His skin was cyanotic. Patellar reflexes were elicited despite flexed limbs, forearm reflexes were exaggerated, and some odd muscular reflexes were present. The pupils of his eyes were inalterably dilated even in bright light. He sucked, swallowed and cried out, and withdrew his body when the skin was pinched or heated. Quinine and camphor elicited no taste response, but ammonia vapor caused withdrawal of the head. He began to have convulsions about 20 hr. after birth. These were described as starting in the left arm and then becoming general.

Anencephaly illustrates a gross structural deviation from normal pathways of development manifesting itself early in embryogenesis. The functional disturbances are for all practical purposes the consequence of gross anatomic defect.

### *Hereditary Ataxias*

This group of disorders illustrates the fact that anatomic developmental disorders can appear in a tissue after it has 'grown up' to the adult stage. These diseases of the neuromuscular system of man are collectively called hereditary ataxias by Bell (6) and Schut (28), and muscular atrophies by Aring & Cobb (3) [see also Cobb (10)] and they are more closely related genetically than their neurophysiologic disturbances would suggest. The term 'hereditary ataxia' is a fairly useful generic term because it implies the two major features present in so many of the syndromes. The diseases, which show several patterns of inheritance and expression, may be interrelated by the action of several genes or groups of genes on more than one chromosome. These genes may normally govern the integrity and longevity of a specific constellation of adult neuromuscular structures perhaps by providing specific enzymes essential for these seemingly unrelated tissues. If the enzymes were absent or 'mutated,' they could affect those structures profoundly.

Some of the major patterns of the group of diseases that have received distinct names are Friedreich's ataxia, hereditary cerebellar ataxia, hereditary spastic paraplegia, progressive peroneal muscular atrophy of Charcot-Marie-Tooth, and progressive muscular atrophy. These may be combined in several ways and degrees, or one may appear in fairly pure form and some other findings such as optic atrophy may be prominent. The heredity may be recessive or dominant, and sometimes sex-linked, and in different pedigrees the patterns may develop distinctive characteristics.

The disturbances of function in the hereditary ataxia group are directly related to the degenerative changes in the particular fiber tracts, neuron bodies, peripheral or cranial nerves, or muscles involved. When the posterior columns of deep sensations and the cerebellar pathways are chiefly involved, ataxic patterns predominate. In a given family the age of onset, progress and pattern of the disorder may be very uniform among the siblings.

The hereditary ataxias and related muscular disorders are included here to emphasize the futility of describing congenital abnormalities without also trying to understand their ontogeny. Cobb (10) has said recently: "Several authors have tried to describe new 'diseases' without pathological data and without understanding that in hereditary diseases the genotype (abnormality of the genes) may be relatively constant, whereas the phenotype (clinical manifestation) may vary greatly according to developmental and environmental influences. It is this kind of making of new 'disease entities' and 'syndromes' which has so complicated neurological literature that 'one cannot see the forest for the trees.' This group of neural myopathies should be looked on as one disease with many variants. Many have been already described, but many more will arise and should not then be

listed as new, but as expected and predictable on genetic grounds."

## INBORN ERRORS OF METABOLISM

A number of conditions affecting the development of the nervous system show themselves primarily as abnormal forms of bodily chemistry with or without anatomic abnormalities. They may exist because an enzyme system failed to develop, or they may result because metabolic pathways are present that lead to accumulations of abnormal metabolites. A number of disorders occur in which the histiocytes and other cells continue to manufacture certain fatty substances that in turn may accumulate in the tissues, including neurons, or they may otherwise affect neural function by means which are presently obscure (32). Among these are Tay-Sachs amaurotic family idiocy in which the nervous tissue is selectively affected early in life by the intraneuronal accumulations of gangliosides made by the neurons themselves (22). These accumulations cause degeneration and often destruction of the cells. In the infantile type of the disease, the child shows gradual impairment of vision, then blindness; this is accompanied by mental deterioration progressing to idiocy and paralysis of the limbs and body.

Another developmental abnormality, which becomes manifest in the teens, is Wilson's disease or hepatolenticular degeneration, characterized by an inborn error of copper and alpha aminoacid metabolism. When the disease has developed, there is diffuse gliosis of the brain, especially the lenticular nucleus, and hepatic fibrosis, and a copper-containing pigment discolors the iris. Ceruloplasmin, a plasma protein that binds copper normally, is deficient in these patients and plasma copper may also be low. However what copper is present may be improperly bound and this may be why it is more easily deposited in tissues than normal. Whether this is directly related to the aminoacid disorder (aminoaciduria) is obscure (12, 33).

Still other examples of inborn errors of metabolism in which the nervous system is affected are illustrated by Thomsen's disease or myotonia congenita which is accompanied by some structural defects in other organs, familial periodic paralysis in which a disorder of potassium metabolism is present, pernicious anemia, and myasthenia gravis. There are many others but these are cited to emphasize again the diversity.

### *Phenylketonuria*

This disorder, also called phenylpyruvic oligophrenia, is a disease due to an inborn error of metabolism that has attracted much attention and study (20). It is characterized from the time of birth by various grades of mental deficiency and by the excretion of phenylpyruvic acid in the urine. The condition appears to be caused usually by a single recessive gene. There are no consistently found gross or microscopic structural changes in the nervous system that can be correlated with the mental defect and the only consistently related characteristic (90 per cent) is a blond complexion: fair hair and skin, and blue eyes. Abnormally high amounts of phenylalanine and its derivatives are present in the body fluids and the evidence favors the view that the metabolic error lies in a block in the enzymatic conversion of phenylalanine into tyrosine. Precisely what steps are involved is still debatable. The normal enzyme system that makes this conversion is absent in the liver of phenylketonurics. In normal people but not in phenylketonurics the ingestion of phenylalanine is followed by a brief rise in blood tyrosine-like substances. Isotopically labeled phenylalanine can be shown to be incorporated into the proteins of normal individuals as tyrosine-like substances, but this does not happen in phenylketonurics.

Disturbances of neural function are characterized by mild to severe mental deficiency, that is, low grade intelligence, but there are no distinctive patterns. In exceptional cases the affected individuals can get along outside of institutions and make a living to support a family. About one-third of phenylketonurics show no other nervous system abnormality while another third exhibit such signs as mild muscular hypertonicity, hyperactive deep reflexes, awkward gait, slight tremors and occasional irregular motions. In the remaining third a stooped posture, rigid gait, hypertonic muscles and hyperreflexia may be found, and tremors of the hands sometimes with purposeless movement occur. A variety of other occasional findings are reported but they are too inconsistent to be characteristic. Convulsive episodes are however a feature of phenylketonuria, although the episodes in any given patient are rare.

Despite the fact that phenylketonuria has been a popular subject for study because some aspects of its biochemical genetics are well defined, the relation of mental deficiency to phenylalanine is less clear. Does the accumulation of phenylalanine cause the poor neural function? Or are the mental defect and the accumulated metabolite two different end results of a

common genetic fault? Diets low in phenylalanine sources do appear to have a salutory effect on the condition (9). When the diet is given to some affected children, there is a substantial improvement in mood, behavior, motor activity and responses to other people. When phenylalanine is again given to such children, these improvements are reversed. Beyond this degree of improvement the mental retardation has not been reversed by diet or other therapy. It is quite possible that the synthesis of normal molecular constituents in the developing nerve cells is abnormal from early fetal or embryonal life. The answer to the puzzle may come when a newborn infant who excretes phenylpyruvate is put on a low phenylalanine diet at once. Thus far phenylketonuria has not been present in any individual who has not also been mentally defective.

### *Audiogenic Seizures*

In a number of rodents, violent convulsions may occur when the animals hear loud, high-pitched noises (15). The convulsions are often quickly lethal. Although this behavior is superficially similar in the various animals, and a recognized genetic process lies at the root of many, the mechanism of expression differs. Various environmental factors, such as dietary constituents, drugs and infections, also influence the degree of susceptibility to the seizures. One inbred strain of mice known as DBA 2 has been studied extensively. In these animals the period of susceptibility to lethal sonogenic convulsions is virtually limited to the postnatal age of 24 to 45 days. The genetic situation is that of a dominant, apparently single factor which in more than 80 per cent of cases expresses itself through a response to the sound range usually employed experimentally. A high-pitched sound, such as an air blast or a door-bell, precipitates the onset of rapid running movements, then tonic, clonic and spasmodic convulsions. Depending on the noise (and on the individual) death or recovery results; the fatal reaction may occur in less than 90 sec. A number of antiepileptic drugs, glutamate for example, can raise the threshold for seizures or actually prevent them, while other compounds lower the threshold.

The biochemical disturbance responsible in DBA mice has been related to an abnormality of phosphorylation in the forebrain, probably not in the brain stem (1). Compared with a control strain of mice at age 30 days, oxidative phosphorylation in brain homogenates of 30-day-old DBA mice is substantially reduced, and adenosinetriphosphatase is significantly lower than normal. These and some related indicators of a 'defective' phosphorylative system are present up to about 45 days of age when they are gradually replaced by normal values. The investigators interpret the findings as indicating that the lower threshold for convulsive excitation of the DBA mouse brain is caused by a relative lack of energy-synthesizing processes which normally keep functional activity under restraint.

The chief point of interest about audiogenic seizures in these mice is that they seem to illustrate how an ontogenetic delay in maturation of one part of the metabolic machinery—the formation of certain enzymes in the brain itself—can place the organism in a specifically precarious neurophysiologic position in relation to its environment. The condition may be viewed as a 'transient' inborn error of metabolism. The month-old mouse is in a stage of transition to an adult pattern of highly oxygen-dependent brain metabolism which normally results from an harmonious and synchronous maturation of molecular events. How many analogous situations there may be among vertebrates where asynchronous timing of developmental metabolic processes leads to transient imbalances and temporary neurophysiologic disturbances can only be guessed.

## NEOPLASTIC DEVELOPMENT

A number of developmental disorders express themselves in the form of abnormal growths or frank neoplasms early in life, often being present at birth. Vascular malformations and hemangiomas are among the commonest, functional changes being referable to the part of the nervous system involved by the vascular growth or secondarily affected by impaired blood supply. Tuberous sclerosis is a rare example of a semineoplastic malformative process involving the brain. The occurrence of similar gliomas in identical twins at the same time, although rare, suggests that a developmental disturbance might underlie some of these growths.

### *Retinoblastoma*

This rare tumor composed of embryonal neural cells may develop in the retina in infants or young adults (37). Although usually fatal, some tumors are apparently self-limiting, dying out before they spread or metastasize. The disease is due to a dominant gene

which expresses itself over 90 per cent of the time. When the tumor has not killed the individual until after adulthood is reached, reproduction of course becomes possible. From the families of such persons, the genetic data are known (25).

The neurophysiologic disturbances from the tumor are those referable to local destruction of the eye by the tumor, and to invasion of the brain or adjacent nerves. There are of course first focal defects in the retinal field followed usually by loss of vision in that eye. Other alterations of neural function would vary with the course of the invasive tumor: compression and destruction of the nerves of the orbit, destruction and compression of the anterior parts of the brain, and increased intracranial pressure.

The example is chosen to illustrate still another way in which neurogenesis may go wrong. In this instance a genetic situation expresses itself as a destructive neoplasm, perhaps first passing through a stage of nonneoplastic structural malformation.

## EXPERIMENTAL CONGENITAL ANOMALIES

In a sense, any form of abnormal development brought about by experimental embryologic extirpative techniques or other procedures is a congenital anomaly. In many instances the difference between spontaneous and induced structural abnormalities is simply a matter of whether the procedure was the result of an 'accident' or designed by an experimenter. There are two areas of experimental neuroembryology that might not ordinarily come into a discussion of congenital anomalies but which deserve mention because they illustrate some most interesting aspects of abnormal neural functional development. They are *a*) the effects of heteroploidy on the ontogeny of the brain and *b*) the degree of functional specificity that is built into the structure of the nervous system early in its development. This second, however, is so much a part of experimental neuroembryology and 'normal' developmental neurophysiology that it will not be reviewed here. Reference has been made to the work of Weiss, Sperry and Stone in the brief summary of neural development. Suffice it to say that the work emphasizes that what we call 'abnormal' development is as much governed by ontogenetic laws as the normal.

### *Heteroploidy in Salamanders*

The phenomenon of how ploidy in development can affect the function of the nervous system is sufficiently interesting and unique to justify its separation from other 'structural' disorders. In the vertebrates generally it is usually taken for granted that the normal complement of chromosomes in somatic cells is diploid, that is twice the (haploid) number in the sperm or egg. This is certainly approximately true, although in adult mammalian cells variations from cell to cell are known to occur and variation in some degree may be the rule. Parthenogenesis, too, occurs not only in lower vertebrates but in birds and mammals including, probably, man (in the latter, however, parthenogenetic embryonic development would not be credited if it progressed beyond the earliest stages). In lower vertebrates animals may develop with not only the normal two sets of chromosomes but with three sets (triploidy), four sets (tetraploidy) and even up to seven sets. Fankhauser and his associates have studied the general consequences of heteroploidy in development (13) and particular aspects of neural function in such abnormal animals (14).

Polyploid animals may occur spontaneously among salamanders (*Triturus viridescens*), and animals with three sets of chromosomes can be induced by exposing fertilized eggs to a temperature of 36°C which suppresses the second maturation division. What is of interest here in polyploid salamanders is that the individual body cells are larger than normal, but the whole animal is only normal size. As a result there is actually a smaller total number of cells in the body, perhaps something like two-thirds the normal number. Cross-sections show this to be true in the triploid brain which is normal size but obviously has less cells. (With increasing numbers of sets of chromosomes, there are proportionately even fewer cells, although the discrepancy does not advance on straight numerical scale.)

Fankhauser and his co-workers compared the learning capacity of triploid salamanders with that of normal diploid animals. They were subjected to a swimming course involving a choice between a reward and a noxious stimulus, and their ability to differentiate between the two was tested. The triploid animals were less gifted than their brothers in this respect, and the evidence gathered pointed to a lesser number of brain cells as being the principal factor responsible for their deficiencies.

Whether heteroploidy is ever a significant factor in the development of abnormal function of the nervous system in higher vertebrates is presently unknown. It serves however as still another example of how developmental processes can express themselves in terms of deviations from normal neural function.

## CONCLUDING REMARKS

This presentation of some aspects of disturbed neural function in the presence of congenital anomalies in vertebrates was aimed to show that the abnormalities are a product of the developmental processes and that they may appear in a wide range of forms with ultimate expressions at the gross structural, physiologic or biochemical level. They may appear at any stage of development for development spans the life of the organism. An extraordinary variety of mechanisms may be involved in the processes that lead to the malfunction, extending from patterns that are primarily the result of uncomplicated genetic situations to destructive accidents to the embryo, neoplasia and bizarre variations in chromosomal ploidy. The analysis and description of neurophysiologic disorders as they appear in the end stages of anomalous developmental processes may be quite accurate and scientific, but an understanding of how they may have evolved makes the analysis much more rewarding.

## REFERENCES


1. Abood, L. G. and R. W. Gerard. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 467.
2. Anastasi, A. *A. Res. Nerv. & Ment. Dis., Proc.* 33: 67, 1954.
3. Aring, C. and S. Cobb. *Medicine* 14: 77, 1935.
4. Ballantyne, J. W. *Manual of Antenatal Pathology and Hygiene*. Edinburgh: Green, 1902, vol. 2.
5. Beach, F. A. *Hormones and Behavior*. New York: Hoeber, 1948, chap. xii.
6. Bell, J. In: *The Treasury of Human Inheritance*, edited by R. A. Fisher and L. S. Penrose. London: Cambridge, 1948, vol. iv, p. 343.
7. Benda, C. E. *Developmental Disorders of Mentation and Cerebral Palsies*. New York: Grune, 1952.
8. Bergquist, H. and B. Källen. *J. Comp. Neurol.* 100: 627, 1954.
9. Bickel, H., R. J. Boscott and J. Gerrard. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 417.
10. Cobb, S. Discussion in J. W. Schut (28).
11. de Busk, A. G. *Advances Enzymol.* 17: 393, 1956.
12. Denny-Brown, D. *A. Res. Nerv. & Ment. Dis., Proc.* 32: 190, 1953.
13. Fankhauser, G. *Quart. Rev. Biol.* 20: 20, 1945.
14. Fankhauser, G., J. A. Vernon, W. H. Frank and W. V. Slack. *Science* 122: 692, 1955.
15. Ginsburg, B. E. *A. Res. Nerv. & Ment. Dis., Proc.* 33: 39, 1954.
16. Goldschmidt, R. B. *Theoretical Genetics*. Berkeley: Univ. California Press, 1955.
17. Grüneberg, H. *Genetics of the Mouse*. The Hague: Nijhoff, 1952.
18. Herrick, C. J. *The Brain of the Tiger Salamander*. Chicago: Univ. Chicago Press, 1948.
19. Hicks, S. P., B. L. Brown and C. J. D'Amato. *Am. J. Path.* 33: 459, 1957.
20. Jervis, G. A. *A. Res. Nerv. & Ment. Dis., Proc.* 33: 259, 1954.
21. Kallmann, F. J. *Heredity in Health and Mental Disorders*. New York: Norton, 1953.
22. Klenk, E. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 297.
23. Lashley, K. S. *J. Nerv. & Ment. Dis.* 88: 733, 1938.
24. Matson, D. D. *A. Res. Nerv. & Ment. Dis., Proc.* 34: 59, 1954.
25. Neel, J. V. and W. J. Schull. *Human Heredity*. Chicago: Univ. Chicago Press, 1954.
26. Penrose, L. S. *Biology of Mental Defect*. New York: Grune, 1954.
27. Saint-Hilaire, G. *Ann. sci. nat.* vii: 357, 1826.
28. Schut, J. W. *A. Res. Nerv. & Ment. Dis., Proc.* 33: 293, 1954.
29. Sperry, R. W. *Quart. Rev. Biol.* 20: 311, 1945.
30. Sperry, R. W. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 74.
31. Stone, L. S. *Ann. New York Acad. Sc.* 49: 856, 1948.
31. Thannhauser, S. J. *A. Res. Nerv. & Ment. Dis., Proc.* 32: 238, 1953.
33. Uzman, L. and B. Hood. *Am. J. M. Sc.* 233: 392, 1952.
34. Waddington, C. H. *Principles of Embryology*. New York: Macmillan, 1956.
35. Weiss, P. A. *J. Comp. Neurol* 66: 181, 1937.
36. Weiss, P. A. In: *Analysis of Development*, edited by B. H. Willier, P. A. Weiss and V. Hamburger. Philadelphia: Saunders, 1955, p. 346.
37. Weller, C. V. *Cancer Res.* 1: 919, 1941.

# Neurophysiology: an integration (molecules, neurons and behavior)

R. W. GERARD | *Mental Health Research Institute, Departments of Psychiatry and Physiology, University of Michigan, Ann Arbor, Michigan*

CHAPTER CONTENTS

. . . there is something wonderful in the idea that man's brain is the greatest machine of all, imitating within its tiny network events happening in the most distant stars, predicting their appearances with accuracy, and finding in this power of successful prediction and communication the ultimate feature of consciousness. . . . I see no reason to suppose that the processes of reasoning *are* fundamentally different from the mechanism of physical nature. On our model theory neural or other mechanisms can imitate or parallel the behaviour and interaction of physical objects and so supply us with information on physical processes which are not directly observable to us. Our thought, then, has objective validity because it is not fundamentally different from objective reality but is specially suited for imitating it—that is our suggested answer. It sets no crabbed limit to the attempt of thought to understand and express the universe.

CRAIK, K. J. W. *The Nature of Explanation*, p. 99 (49).

The picture of skilled performance built up by modern researches is one of a complex interaction between man and environment. Continuously the skilled man must select the correct cues from the environment, take decisions upon them which may possibly involve prediction of the future, and initiate sequences of responses whose progress is controlled by feed-back, either through the original decision-making mechanism, or through lower-order loops. The processes of filtering the information from the senses, of passing it through a limited capacity channel, and of storing it temporarily are only part of the total skilled performance. But they are of the same general nature as the other processes involved, and harmonize with the broad view of skill which is now developing.

BROADBENT, D. E. *Perception and Communication*, p. 295 (32).

## INTRODUCTION[1]

### *State of the Science*

LIVING IS SEEKING. Living things ride a double rail through time. The organism (or org or system) at any instant possesses, as a product of its individual history, a more or less unique heterogeneity which reacts to its present and its expected environment. Early in evolution the presenting physical surround was salient. Later, emphasis shifted to the biological and, especially in man, to the future and the social aspects of the environment. The outcome of actions as good or bad, adaptive or nonadaptive, is judged in terms of development of the individual or evolution of the species projected against the future environment. There is always some type of goal or 'desired' direction at any time; but since this is as true for a drop of water 'seeking' the sea or a population evolving adaptive structures as it is for a seedling 'seeking' the light or a rat learning a maze, volition and freedom are not at issue.

So living is riding the rails of the expected and the desired, a double projection from the existing, an unending tracking performance based on a probability calculus [see Vickers (284)]. Whether a man actually sets his goals more than does an ameba is still debated, but he surely exhibits more conscious foresight in pursuing them. A civilized man in his psychosocial community faces wide divergence of the expected from the hoped-for or feared, with the intricate overtones of behavior involved in enculturation and self-restraint, the psychiatrist's superego. This full

[1] This chapter is partly a review of reviews—the many fine chapters in this *Handbook*—but is more a personal essay. I have read, with great profit, all available manuscripts (several were not), have made voluminous notes and have drawn freely on these materials in my own contribution. (Much of this initial digestion was accomplished while I was guest praelector of the University of St. Andrews, Scotland—for which opportunity I am grateful.) *Handbook* chapters have been used liberally as references for general or particular statements. (They are consistently referred to in the text by the authors' names without reference numbers.) On the other hand, it would have been oppressive to cite each chapter on each point to which it related; so the references are somewhat impressionistic, depending on which was in mind as I wrote. The same selection, based on undisciplined recall, has influenced the use of other citations. Work that remained long in my mind or was recently encountered in far from systematic reading or conferring has been mentioned. That my own writings have received undue emphasis will thus be understood and, I hope, forgiven. [In this, Dr. Gerard has had our full encouragement. — Editors.] Needless to say, the bulk of classical work in neurophysiology is cited in other *Handbook* chapters and does not receive further note here; many great names do not appear in the list of references. This chapter, rather than being a hopeless attempt at restating the findings of a generation or two of investigators of the nervous system, is the residue—dare I say, engram—of my own exposure to the work and thought of many colleagues and of some teachers and intimate friends in this goodly band of explorers. I thank many who have contributed to it directly or indirectly. It, in turn, may help contribute a flavor to the intellectual food in the *Handbook*.

richness of behavior must some day be explainable (although, like a particular storm, not necessarily in unique detail) in terms of neurophysiology and, later, of neurochemistry. There have been marked recent advances, both in characterizing the behavior to be explained and in developing neural models to explain it.

THE MACHINE. Knowledge of the nervous system has come a long way from ancient times when the soft gray stuff that filled the calvarium was regarded as a reservoir of nasal mucus en route from its source in the pituitary through the cribriform plate to its sink in the nose. Yet it was only three centuries ago (1660) that Schneider proved this view erroneous. First the anatomist, acting almost as a taxonomist, identified and named the major bumps and hollows, the gray islands and white channels. The primitive physiologist or pathologist soon laid down the rudiments of physiological anatomy by observing the more obvious consequences of irritating or damaging one part or another. Later, the microscopical morphologist, with his hardening fluids and staining tinctures and microtomes, described cells and fibers, connected them with each other (with a great assist from experimental embryology), and is still proceeding with the enormous task of diagramming the complete wiring circuits in a city of 10 billion inhabitants, extended in all three dimensions and reduced to the size of a soft ball. The chemical morphologist, identifying and locating the molecular elements, came much later and his studies are largely for the future, along with those of the chemical traffic of the living machine at rest or when active. Analytic neurophysiology, concerned with the mechanisms of action rather than with their loci, is an offspring of this century and remains in the early exponential growth phase; analytic developmental neurology is still being born. It would seem to behoove us, then, to be hopeful rather than impatient if today we can only adumbrate the processes whereby the organ of mind plays the tunes of behavior.

BEHAVIOR. Behavior is also seen today in a vastly different setting than a few decades back. Just as the picture of inheritance in terms of compressed homunculi in germ cells gave way to one of interacting developmental processes, so did that of behavior relinquish the anima or soul or consciousness, a mental homunculus that exercised volition, in favor of interacting streams of information. Laboratory and life experiments are defining the quantitative relations between the amount, kind and multiplicity of input of information and the speed, precision and complexity of performance—including the reports of subjective experience. The studies distinguish between the properties of input and output transducers, transmitting channels, coding schemata, memory stores, computer elements and even selector (or valuing) devices. Attention, perception, ideation, reason, performance and the like are being given precise and operational meanings. It is one matter to offer a neurophysiological interpretation of a slower response to a more difficult discrimination, but quite another to develop a neural model that gives reaction time as the logarithm of information (proportional to the number of bits presented), or 0.12 sec. as the time per bit for each input or output decision, or perceptual capacity as seven bits in the first dimension of 'discrimination space,' fewer in successive dimensions. The integrative action of the nervous system, the handling of allied and antagonistic situations, is being examined as thoroughly at the level of language and logic as it was earlier at the level of spinal reflexes, and appropriate brain mechanisms must be elaborated to account for the new rich phenomena.

COMPUTER MODELS. The great computers and the attendant development of mathematics of relationship (rather than of magnitude) will aid in model building as the study of neural behavior has served in understanding computers. The power sources of muscles and of cranes and like social effectors are unrelated, but both the musculoskeletal and the wire-strut systems obey the same laws of mechanics. The photochemical processes in eye and camera differ, but the optics are the same. The programming and storing and decision-making mechanisms of brain and computer have perhaps nothing in common, but the insights from information theory and set theory, from stochastic analysis and topology, from queueing theory and probability theory play freely in both domains.

Aside from the use of these rapidly evolving 'social brains' to simulate various models of a nervous system, or to solve particular equations applied to actual operations, the development of computer theory has exhibited sharply the processes involved in man's decision-making. Attempts made by Ledley & Lusted (169), to build a computer program for the diagnosis of disease, for example, have involved the following steps: building a table of all signs and symptoms on one axis, of all diseases on a second, filling all squares with a plus or zero, and committing this background information to memory. Further,

to give appropriate weight to each entry, the probability of the particular observable occurring in the particular disturbance is programmed—headache is the rule with a brain tumor, the exception with a dislocated disc. Then some value ratings are attached to the decisions: a positive error in diagnosing appendicitis and operating, rather than choosing 'indigestion' and giving a soothing potion, is more serious than is a similar positive error in diagnosing cholecystitis and prescribing bed rest; whereas a negative error, in diagnosing appendicitis or cholecystitis as 'indigestion' is more serious in the reverse order. Later, the initial settings of the machine are readjusted in terms of the feedback from its own experience—corrected for clinical judgment, autopsy findings and the like—so that its performance steadily improves. The initial information is supplied by human judgment from books, records and panels of experts, and no sensible person would prefer the computer's diagnosis to that of his doctor. But, in time, the collective wisdom of man could be integrated in a single instrument and enriched by its experience at a rate impossible to a single brain. Then the physician will seek aid from it.

Another computer, properly programmed and given the axioms of the 'Principia Mathematica,' has solved over three fourths of the first 50 theorems (219, 220); a third can learn to discriminate patterns without prior instructions (252); a fourth behaves directly as a neuron assembly and serves to test parameters (249). One is being developed (250) to simulate a society (or a brain, for that matter) with originally naive members and loose connectivities that develop special roles and organizations while achieving effective performance. Indeed, learning by a system may involve little learning by its components—whether a brain (203) or a structural group (Bavelas, personal communication) or, for that matter, a gene pool. With computers learning to learn, the epigenetic invention of life, great advances are imminent. [See also von Neumann (287), Simon & Newell (264) and Green (127). A valuable further reference on processing neuroelectric data is Technical Report 351, Massachusetts Institute of Technology Research Laboratory of Electronics, 1959, by Rosenblith and others.]

My hope in this essay is to help direct the attention of neurophysiologists, especially of those starting their careers in formal physiology departments, to the mounting challenge and opportunities in this sector of behavioral science. Behavior is rooted in the metabolism of neurons and flowers in the great imaginative creations of mankind. Understanding it will demand the pooled skills of many presently disparate disciplines.

### *Architecture of Knowledge*

LEVELS. A later section of this chapter will consider the nervous system at different levels of organization from that of gross anatomy to that of molecules, so a brief over-all consideration of general level properties may be helpful. Any system with sufficient identity to permit study has some sort of a boundary which separates it from its environment. This environment may itself be a larger system in which the system given attention is an element, or the environment may be entirely external to any organization of which the system is an integral part. Internally, also, the system is composed of discriminable elements, not necessarily all alike, which may themselves be subsystems containing further subordinate units.

It has proved helpful in considering the broad scientific scene to plot the levels on an ordinate axis and the attributes of systems on the abscissa. The levels that concern biology run from the molecule up through the organelle, cell, tissue and organ, organism and small hereditary or ecological group, to a larger society or ecosystem. The relevant attributes are 'being' or architecture, 'behaving' or function and 'becoming' or development. The table (fig. 1) thus generated (115) has proved useful in many ways. For one thing, knowledge has started with man's sensory experience, roughly at the individual level and in the descriptive structural column; it has then spread, as a series of expanding semicircles, horizontally to function and development and vertically to constituent or collective units. This is exemplified in the history of our knowledge of the nervous system which has moved from structure to function to development, and from gross anatomy to gray centers to neurons, to membranes and Nissl granules and molecules. Modern concern with neural organization has moved from the structural to the dynamic to the learned, as appears also in this chapter.

FUNCTIONAL UNITS. The structural entities, in the first column, regularly obtain earliest attention; the functional ones, in the second column, appear with advancing sophistication. Neurophysiology clearly falls in the second column and extends from cell to individual, trailing into neurochemistry at the molecular level and heading into individual and group psychology at higher ones. Social roles, indi-

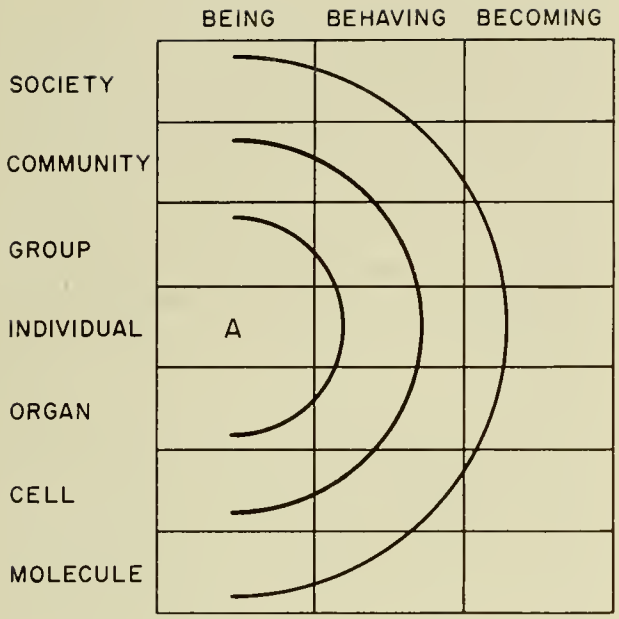



FIG. 1. The architecture of knowledge in biology. Levels of organization are represented on the ordinate axis, attributes of these levels on the abscissa axis. See the text for further explanation.

vidual behavior patterns, reflex responses and nerve impulses are physiological or functional units, and so of interest to the neurophysiologist. He is concerned with thresholds and spike magnitudes, with facilitation and inhibition, with summation and fixation, with synchrony and reverberation, more than with nerve fibers and cells. Just so the enzyme chemist is occupied with catalytic action and rate of change more than with molecular structure, and the ethologist deals with animal behaviors rather than animal bodies. Of course, structure underlies all function, and a change in kind or number or position of constituent units—right down to the component molecules and atoms—must carry any change in functional state. Nevertheless, the immediate correlation of an experimental variable may be only with a functional alteration.

We know that anesthetics knock out consciousness; we do not yet know the chemical or anatomical (or even neurophysiological) intermediate steps. We know that psychoactive drugs alter mood, but do not yet know how or where they act. It is the hope of most workers that specific chemical agents, by attacking some system related functionally rather than structurally, will help the functional dissection of behavior. The point is perhaps best illustrated by the legitimate insouciance of the neurophysiologist—who obtains beautifully constant action spikes from a nerve isolated for hours—in the face of the anguished cries of the cytologist who sees the progressive distortion of the visible nerve structures during this same time. Similarly, as shown by Tobias (280), a nerve fiber almost digested by proteolytic enzymes may still conduct well, while one less altered visibly with lipolytic ones may be completely blocked.

The table has proved useful, further, in understanding and in projecting experiments to recognize certain common factors (as well as the obvious differences) between the levels in a given column. Thus one aspect of behaving is the response to an abnormal input, a stress of some kind. Two general types are clear (115): a quantitative abnormality, as in input-overload (excessive quantitative demands on perception and performance) or input-underload [sensory deprivation, studied by Miller (211)]; and a qualitative shift [slightly differently-patterned antimetabolites which block cell enzymes, or slightly distorted perceptual patterns which confuse meaning in language or other symbols, as pointed out by Gerard, Jackson & Miller (unpublished observations)].

MATERIAL TRACES. Behavior is certainly dependent upon structure and structure, upon behavior; but this does not lead to a meaningless potpourri. Behavior at a given level depends on structure at the subordinate level; and this, in turn, is the product of such an intense or repeated past behavior at the next lower level as to have left behind irreversible rather than reversible change. When the table of figure 1 is rolled into a cylinder, a 'causal' spiral is seen ascending the levels as it moves from becoming to being to behaving.

For the nervous system, those molecular actions that led irreversibly to macromolecules and related cell constituents produced the ultrastructures of cells—the membranes and particulates which control the basic physicochemical behaviors of neurons. Neurons sprout processes and form junctions in terms of their own experiences during functional development, leading to the visible structures of gray nuclei and fiber paths, and through them to integrated individual behavior. Individual experiences, impressing structure on the nervous system and the personality, give new structural intricacies to groups and organizations which in turn determine their collective behaviors as supraindividuals or epiorganisms.

It is impressive that all levels of living systems—from the duplicating molecules of heredity, through the developing brain, to the evolving species or the

maturing institution—depend on an epigenetic rather than a preformed mechanism for growth and elaboration. The particular machinery of polynucleotide or protein synthesis has no surface relation to that for building new neuron connections or to that for setting new sociograms in a business firm. Yet in all cases there exist: first, some initial organization, a template of sorts which guides the pattern of the new formation; and second, some operational rules that lead to kinds of outcomes, with the particulars left to the detailed conditions of environment-system interaction. This is the great invention underlying all progressive change in living systems, the epigenetic mode. Only in a primitive way do present artifacts learn (12, 13, 290); but, as noted, they have begun to learn to learn.

INFORMATION. Given a material system, with its supra- and subsystems and with its material and functional units, there arise the questions, first, of the influences that operate between units, involving the kind and structure of the connections between them, and second, of the mechanisms by which changes are induced. Across the boundary of a system or a unit may flow material, energy, and information—the long-recognized biological factors of transportation, mechanical influence and transmission. The nervous system is overwhelmingly concerned with information; but the flow of substance and energy is involved in its maintenance and responses, and transducers are operating throughout the central system and its receptor and effector attachments to effect transformations between mechanical, electrical, chemical and other changes, and the nerve messages that initiate or result from these.

The transform functions relating input to internal change to output are being intensively examined for all sorts of flows through all sorts of systems. The action spectrum of chlorophyll, the frequency response curve of nerve, the conditioning patterns of rats, and the performance of a submarine and its crew under depth bomb attack each involves the appropriate transform functions; but the formal problem is alike in all, and some common model formulations and analytic procedures are proving widely useful. The fixing of experience—in genes and proteins, in cellular immune reactions, in neural engrams and individual memories, in group customs and libraries—is also formally similar (104, 115). But the exploration of organization, long restricted to structure, is now bursting into the area of action; patterns in time and space, and their interactions, involved in handling information, are now a focus of research.

HOMEOSTASIS. All dynamic systems that endure have homeostatic mechanisms through which they are able to marshall their resources in counteracting disturbances and re-establishing, or moving towards, the initial equilibrium. They also have mechanisms for altering with experience and shifting their state (including probability expectations) as a result of it, some sort of learning and remembering. Negative feedback is an outstanding homeostatic device of the nervous system; accommodation, adaptation and modification are ways of adjusting to environmental change.

Finally, every system of interest here has a range of behavioral possibilities that, however fully determined, appear as choices or decisions. There is 'goal-directed' behavior at the cellular level in morphogenesis—including the 'seeking' of the field of innervation by growing nerve fibers (291); at the organ level in development, seen elegantly in the series of activations of neural hormones in insect metamorphosis (294); at all levels, from molecule to species, as a form of learning or microevolution (104). Molecules may polymerize in one or another pattern; neurons may fire or not; locomotion may begin with the right or left leg, and it may be directed to objective A or B; species may solve an environmental problem by a variety of adaptive answers. In the nervous system, the synapses are the 'points of decision' and their 'table of organization' is of major importance. Through this organization information flows in and instructions flow out, and end patterns of consciousness and behavior result. An army or a computer functions in a comparable manner.

## SETTING OF THE NERVOUS SYSTEM

### *Psychology and Physiology; the Black Box*

It is an important decision in research strategy to decide, in attacking any given problem, at which level and to what type of unit within it attention will be directed. The bitter arguments between holist and reductionist approaches are largely due to a failure to recognize these possible choices. The psychologist, establishing stimulus-response relations for a rat or a man, is proceeding as did the physicist in relating electric currents to magnetic fields, or the neurophysiologist in relating the discharges of a neuron to the presynaptic barrage. Analysis of mechanisms always leads the query to a lower level—organism behavior to neurons, neuron behavior to molecules and ions—but work is sound and necessary within as well as across levels.

It broadens the perspective to realize that interviewing an individual in a group in order to understand the group's behavior, or leading from a neuron cluster to understand that of a brain, or polarizing a neuron through an impaling electrode to modify its responses are all maneuvers of essentially the same type.

ENTERING THE ORGANISM. The living organism is interesting in terms of its behavior. The higher the organism, the more rich and variable its repertoire of actions and the more cues to action does it discriminate in its environment. Psychology has dealt primarily with the whole organism as a 'black box' giving responses to stimuli, able to receive, process and utilize information. The properties of the box, the throughput, were inferred from the relation of output to input; and certain molar relationships were established. The vast studies of sensory physiology and physiological psychology have dealt with the mechanical or chemical transducers which transmute or encode patterns of light and taste, chemically, and of sound and touch, mechanically, into patterns of inflowing messages in bundles of nerve fibers; the vast studies of motor and neurosecretory physiology have been concerned with the converse decoding or transmutation of outflowing patterns of nerve messages into mechanical and chemical patterns of performance. The discovery of action potentials, and the development of instrumental and manipulative techniques that made it possible to tap the nerve impulses to and from the central nervous system, enabled investigators to enter the organismic black box and study directly the input and output of the central nervous system.

Such fractionation of the total problem also made it possible to focus investigation in other ways. In one direction, with input and output of the single transducer directly observable progressively down to the level of the individual unit, progress was rapid in obtaining the transform function and the physicochemical mechanisms of the various receptors and effectors. In another, the entire body could be examined directly as an environment of the nervous system—stimuli from the body initiating afferent messages and efferent messages acting upon it, and negative feed-back loops from the nervous system controlling the receptors and the effectors, largely by regulating their sensitivity and modulating their output. In this case it also proved important, to a far greater extent than for the external environment, to recognize that the messages are not exclusively nerve impulses but include as well specific substances, hormones or humors, which may act on or be produced by the nervous system at any station of the input, throughput or output sequence. Thus, metabolism may lower oxygen or raise carbon dioxide in the blood to carotid chemoreceptors or to medullary neurons; catechol amines may be liberated from brain-stem structures or from adrenal medulla (von Euler); a rise in plasma osmotic pressure may release antidiuretic hormones from the hypothalamus; the hypothalamus controls the anterior pituitary, even to the extent of differential sex maturation (Harris); food or hormones or temperature specifically alter activity of appropriate neuron groups (Ström, Stellar); and so on.

ENTERING THE BRAIN. The initial problem of stimulus and response of the organism now reappeared in the refined but similar form of input and output to the central nervous system. The same basic procedure, of entering the inner black box, again produced great rewards. By following incoming messages with probe electrodes for evoked potentials, and by initiating impulses with electrical or chemical stimuli, or blocking them with anatomical lesions or chemical or polarization depressions, the functional connections and transform functions of brain regions and nuclei, down to the single neurons, are being explored intensively. Here the problem in one sense is much simpler because (except for the chemical messages and possible decrementing impulses) the inputs and outputs at some distance are all basically similar nerve impulses; but this very uniformity throws the weight of specificity on variations in pattern rather than in kind of signal and so raises the problem of coding and decoding in its purest form. This will be considered later.

INTERACTING UNITS. The synaptic system (which includes the specialized pre- and postjunctional components as well as the actual area of contact, and even the interaction of several of these at, say, an axon hillock) is thus a decision point to which information converges and from which instructions emerge. Here, individually and collectively, the output is a nonlinear and variable function of the input, being determined not only by the total contemporary input, but also by past activations, by current physiological state (a resultant of the chemical and electrical field in which it lies and the chronology of its more recent activities) and by such unanalyzed microevents as result in spontaneous rhythms or irregular threshold fluctuations. It is no accident that in neural evolution the rapid and accurate conduction in an unbroken nerve fiber has been so little used to

replace the slow and less dependable junctions. Speed and precision have been eschewed for richness and variability, and the nervous system has gained freedom between stimulus and response in time, intensity and pattern.

SYSTEM PROPERTIES. At each level of living systems, from membrane through neuron to brain and group, and for nonliving simulacres, from torpedo to computer, there are, then, certain organization and action properties. For each, it is important to work out the architecture, to identify significant units, and to trace the kinds and patterns of their interrelations. For each, it is important to examine the flow, particularly of information, and the mechanisms for coding, storing and utilizing it. For each, the self-regulating and goal-seeking activities must be identified, and the decision-making processes analyzed.

The problems of neurophysiology thus resolve themselves into the properties of the individual units and the mechanisms and patterns of interaction of these units, into the dynamic attributes of the synaptic system and into the mechanisms of interaction of masses of neurons. The problems of physiological anatomy of the nervous system become those of the actual table of organization — the degree of centralization relative to local autonomy underlies the decision-making sequences (a sort of functional topology) and provides the functional significance of the actual spatial disposition of neuron clusters and interconnections. Finally, anatomy and physiology merge in neurochemistry at the level of molecular architecture and traffic. In the following sections, the nervous system will be examined from such viewpoints.

### *Neural Evolution*

COMPONENTS. A yeast cell and a cortical neuron contain many interchangeable complex molecules and engage in highly similar chemical changes. The basic metabolic paths and pools are alike, so that the processes underlying dynamic equilibrium or maintenance have not changed importantly during evolution. Similarly, for the patterns and mechanisms underlying specific synthesis, the genetic and other synthetic processes have been carried forward from microbes to mammals. This is not so for adaptive amplification, the handling of information, and the repertoire of experiencing, integrating, and behaving. Organisms are rated from low to high on a scale that roughly fits the richness of behavior which parallels the development of the nervous system. If living differs from nonliving in having learned to manipulate energy, as man with fire is to man without, then the higher animals differ from lower organisms in having learned to handle information, as culture with language is to life without.

Starting with familiar molecules in relatively simple patterns, animals have invented new substances and created intricate organizations so that their capacities for using information have increased explosively. The reacting elements of reception, conduction and transmission, and response were pretty much perfected early in evolution. Regularly layered molecules, able to generate oriented potentials, are alike responsible for reception, as in rods (Wald); for conduction, in nerve fibers, and transmission, as in the junctional generator potentials set up in end plates (Fatt) and presumably in postsynaptic membranes; and for responses, as of muscle fibers and electroplaques. Such basic elements seem to have reached their full development with the appearance of vertebrates and arthropods (e.g. Autrum). The human eye may be a better all-round instrument (Hartline), but it is not sensitive to ultraviolet or polarized light nor is it able to resolve high speed movement, as are some insect eyes, and it has poorer nocturnal vision and acuity than other vertebrate eyes. The pit viper has a better temperature sense; the bat, a wider range of hearing; the dog, a superior sense of smell; various fish, a better taste and an electrical sense; birds, superior cues for orientation; and so on. The nerve impulse, the synaptic mechanism, the muscle machine are essentially alike in frog and physiologist. Nevertheless, mammals excel their humbler relatives in the range, sensitivity, discrimination and capacity in receiving information from their environment; and in the speed, control and repertoire of their behaviors in responding to such information. This advance results from superior patterns in the array of the same elements of the system [cf. Gerard (112)].

PATTERNS. A vast improvement in performance of given elements can be achieved by small improvement in their patterning. Feed-back loops that control receptor sensitivity and inflow channel volume, similar loops that regulate and modulate motor performance, other regulating elements that direct attention or set motor goals, as the gamma motor fibers on muscle spindles, and intrinsic re-entrant loops and assemblies (Jung & Hassler) that permit the shifting of time relations and allow the recent

past to modulate the present—all such improved patterns of organization make for the greater capacities of the higher mammals over lower forms.

It is highly doubtful that investigations so far have revealed all the significant patterns of organization that exist in developed nervous systems; nor is it at all certain that the same basic patterns are used throughout the full range of organisms after the pattern has first appeared. Invertebrates control muscle tension by a vastly different neuromuscular mechanism than do vertebrates (Furshpan), and the gamma motor system works quite differently in the frog and in the mammal (Eldred). Nonetheless, there seems no present reason to assume that the continued improvement in performance by the higher mammals, and particularly by the primates and man, is the result of progressive improvement in neural patterns. Rather, just as the reacting elements seem to have reached their asymptote with the arrival of vertebrates and arthropods, so have the patterns perhaps reached their symptote with the arrival of mammals. The remaining freedom for advance is then in the numbers of usable elements and combinations, rather than in the kinds.

QUANTITIES. The point has been developed elsewhere (117), that a simple increase in number can bring about new dimensions of quality. The game 'Twenty Questions' is utterly trivial when the number allowed is half a dozen, is highly sophisticated when the number is unlimited. Adding more memory banks and programming elements to computers enables them not merely to do more or faster calculations, but also to perform new types of processes. An increased channel capacity in the nervous system permits the handling of more information, of course; but also it permits the more intricate handling of that information. It seems quite probable that the finer nuances of human behavior depend primarily on man's greater store of effective neurons (Bremer). Reversible and irreversible decreases in this store explain many facets of perception, anxiety and psychosis—as will be developed later. A similar quantitative view of the defect in some aphasias has been supported by a study of word frequency distribution, more and more common words being lost with more neuron destruction (Howes D. H., III, & Geschwind, N., personal communication).

VALUE OF THE NERVOUS SYSTEM. Man's value judgment of ranking animals on a behavior scale is supported by a seeming value judgment of the body in cherishing its nervous system. This organ is wrapped in multiple membranes; is floated in liquid, the composition of which suggests a purely supportive function (Davson); and is encased in bony armor—all giving maximal protection against mechanical damage. Carotid receptors help insure a constant supply of blood of proper composition at the portal of the brain, and the state of the bathing fluid is further under precise regulation from central receptors for osmotic pressure, temperature, carbon dioxide, etc., which supplement the peripheral regulators (Schmidt, Ingram, Ortmann). Local vascular adjustments protect against oxygen excess (Schmidt) or deficit (Kety). In addition, a special permeability barrier exists, so that the intercellular milieu of the neurons is doubly protected from outside perturbations (Tschirgi). Only in the vicinity of the special chemoreceptor areas is the blood-brain barrier breached (Ortmann). Moreover, glia cells closely invest neuron elements and must contribute to the fine control of their environment; indeed, there may be essentially no true extracellular space [but see Gerschenfeld *et al.* (122)]. Finally, a fifth to a half (Sokoloff) of the resting metabolism of the body is allotted to a nervous system constituting, even in man, only a fiftieth of its weight; and this expensive organ is maintained relatively well through a starvation period, all other organs except the heart being used as fuel. The nervous system is indeed a well-buffered black box, protected from all inputs save those external and internal ones for which it is specifically coded.

### *Maintenance*

HOMEOSTASIS AND GROWTH. A further topic needing consideration before dealing with the nature, activation and formation of neuron patterns, and the behavioral consequences of these—is the homeostasis of the neural machine. This has already been encountered in connection with the devices evolved by higher organisms to protect the nervous system from mechanical insult and chemical vicissitudes. Now, the existence of a continued protoplasmic flow and the nature of neural metabolism, including its magnitude, substrates and uses, need attention. Later sections will consider the relation of metabolism to transmitters and drug action, to proteins and nucleins and information coding, to ions and the maintenance of membrane potential and threshold levels and conduction, and to the control of rhythmic electrical beats via a trip mechanism.

The early suggestion that a severed nerve fiber

degenerates for lack of enzymes reaching it from the cell body [see Gerard (83)] has been supported by extensive evidence (296) that there is indeed a steady movement of particular substances (258), even of synaptic vesicles (282), if not of the entire protoplasm, peripherally along each nerve fiber (291). This rate of movement is similar to the actual rate of regeneration and demands, for the long fibers, a daily synthesis by the perikaryon of new protoplasm equal to three times its own volume. Such rapid turnover also relates to the character of the cell nucleus, the rapid changes in Nissl substance and other nuclein material, the high energy requirements, and the movement of transmitter and other neurohumoral substances along a nerve fiber. Neurons and nerve fibers continue to function quite well after several hours soaking in ribonuclease [RNA is gone on fixation, but the time of enzyme penetration is not established, according to Maynard (personal communication)] or after exposure to proteolytic enzymes (280); yet certain nucleotides, uridine triphosphate and cytidine triphosphate (78), and phospholipids (217) seem necessary to maintain neurons in a functioning state. It is of some interest that these nucleotides, which are concerned with the synthesis of phospholipins and of galactose and galactolipins, rather than guanosine triphosphate, concerned with protein synthesis, have proved important.

METABOLISM. *Amount.* For peripheral nerve, the energy turnover per unit of protoplasm is little more than that for striated muscle, but that of central nervous system [70 per cent of which is due to neurons (Tower)] is 20 to 30 times greater—perhaps to maintain the vigorous continued growth. Under maximal driving conditions oxygen consumption is about doubled for nerve (85) and also brain (Sokoloff), but oxidative phosphorylation may be decreased (Abood). The active metabolism of the nerve fiber can be blocked with preservation of the resting level, and such a poisoned nerve can conduct for hours (31, 58; see also McIlwain for similar block of active metabolism of neurons). This is reminiscent of the convulsive activity of a perfused brain which proceeds with no carbohydrate usage nor increased oxygen consumption (Abood); but it is not the same since, in the nerve, glucose is not even the primary fuel of choice. It should be stressed that the maintenance of resting metabolism is different qualitatively and quantitatively between nerve fiber and cell body and also from the extra metabolism of active functioning (Abood).

*Fuel.* Neurons have special relations to glucose and to glutamic and aspartic acids. These latter are especially rich in brain and function in transamination, related to gamma amino butyric acid—one of the presumptive transmitters or modulators of inhibitory impulses (247) and to potassium concentration in neurons (McIlwain). Glucose, normally the ultimate fuel for neurons as a whole, is not essential for the nerve fiber nor, immediately, even for the cell body. Lipoprotein and nucleoprotein materials, partly in microsomes, are reversibly lost during physiological activity of neurons and can support such activity for hours. Normally restoration is achieved via glucose oxidation, but this may well be violated in von Gierke's glycogen disease, in extended hypoglycemia, and under conditions of artificial perfusion [compare Gerard (106), Geiger (78) and Rinkel & Himwich (246), as well as the chapters by Sokoloff and Abood].

*Control.* Ultimately, chemical morphology must determine neuron function, and all influences upon neurons must alter the number or locus of molecules or ions or macromolecules of various types. The locus can be altered by currents, permeability changes and the like. A given cell or substructure is moved from an existing steady state of equilibrium only by the change of concentration of substances at its surface, by diffusion from or to the surrounding or the inner phase, or by migration under a newly formed potential gradient. All other events must be secondary. A new substance, as a drug or hormone, might reach a cell via the blood stream or, a transmitter or metabolite, from neighboring structures. Substances moved by a changed potential are ions forming a current from a new source to a sink. (Only in special highly structured systems, acting as semiconductors, or resonating molecules are electron movements probably involved; and these are, on present evidence, not primary events in neuron excitation.) Such movements are greatest for small mobile ions, mainly the inorganic ones and perhaps some simpler highly polar $—NH_2$ or —COOH organic ions.

But movement as such is pointless; the concentration of ions in any cube of volume within a homogeneous conductor is not altered by current flow, for equal members enter and leave it. Only where structural heterogeneity exists, such as given by binding sites or a boundary ('membrane') with lower permeability to the ion in question, or as an impermeable dielectric which makes possible a condenser action, can the concentration of ions rise or fall. An altered ion concentration, or ratio, in turn can activate or

inhibit enzymes, disperse or gel colloids, alter folding and linkage of macromolecules, and in general initiate the complex of chemical, structural and dynamic changes that constitute physiological action (84). The close reciprocal influence of membrane conductance and of ion flow and concentration, each highly sensitive to the other (141; Eccles; Tasaki), is probably the secret of conductile tissue. Indeed, the physicochemical interaction between free and structurally fixed ions may control a great variety of biological phenomena (182; Ling, manuscript in preparation).

The amounts can be altered by diet or by excretion or other removal (as citrate binding calcium), but mainly by changes in the rate of production or destruction within the cell or body. If enzyme 1 catalyzes molecule A to molecule B, and enzyme 2, B to C, then inactivation of 1 will increase A and decrease B, and lack of 2, increase B and decrease C. Whether B increases or decreases, its final effect on function could be the same. An increase in B might block some other enzyme and so lead to a deficit in D; but B might, conversely, catalyze D production, in which case a decrease in B would lead to a deficit in D. An increase in D could, of course, equally follow a change in B.

It seems a reasonable guess that, in the course of evolution, each cell or cell region has evolved a pattern of chemical architecture and traffic flow that is essentially optimal to its function, so that imbalance of any important component, either up or down, might be disturbing. Nevertheless, deficiencies of naturally occurring molecules seem more disrupting than do excesses of them, perhaps because more easy corrections are available for an excess, and the ultimate effects of damage are a slowing down rather than a speeding up of metabolism. Probably some deficit in molecules used for structures or for energy is the final bottleneck that prevents normal functioning; but deficits in molecules involved directly in function are more immediate (111).

When a substance is effective on the nervous system in minute doses, it is reasonably certain that it is acting on specific molecules and even at limited loci; when only large concentrations are effective, some general physical action, as one involving lipoid solubility, is more probable. Half a gram of pentylenetetrazol is required to produce convulsions in man; one tenth of a milligram of strychnine does so. Grams of alcohol or ether are required for their effects, but 0.2 mg of LSD produces hallucinations and 0.25 gamma of botulinus toxin can lead to fatal paralysis. It will help progress and limit theorizing if more attention is given to the concentrations at which substances produce their influences on the nervous system.

Neglect of differences between cells, and between cell regions, has also led to much confusion. It is doubtful if, today, we have quantitatively meaningful information on the amount of any substance in any functionally significant locus in any cell in the nervous system (but see Abood). The same is even more true regarding rates of production and destruction, of release from a 'bound' form or from an impermeable compartment and of removal by diffusion or circulation, of precursor storage and movement or of kinase activation and availability, and of like data which are essential to rationalization and prediction at the chemical-physiological, or molecular-organelle, level. Nonetheless considerable qualitative understanding has developed [e.g. Richter (243)], perhaps best exhibited in relation to chemical pathology.

*Pathology.* Specific lacks of some kind underlie the inborn metabolic diseases of the nervous system (both such clear cases as oligophrenia phenylpyruvica and Hartnup's disease and such less clear or debated ones as Wilson's disease or schizophrenia), dietary deficiency diseases (Brožek & Grande), and many actions of drugs and poisons. It by no means follows that such situations are impossible or even difficult to treat. (Interestingly, niacin may relieve amnesia and hallucinations of pellagra, while neural lesions progress downhill, according to Brožek & Grande.) The missing substance may be supplied, a destroyed enzyme supplemented (permeability problems make this more difficult but, again, by no means impossible), or diets adjusted to eliminate a nonmetabolized substance; and various ones of these measures can be and have been used. Consider three examples.

A type of feeble-mindedness associated with the presence of phenylpyruvic acid in the urine was identified in the mid-thirties. During a couple of decades this inborn metabolic disorder of the nervous system has been thoroughly analyzed and brought at least partly under control (74). The phenylpyruvic acid excess is formed from an excess of phenylalanine, an essential dietary amino acid, the normal metabolic path of which, an oxidation to tyrosine, is closed. From tyrosine any number of catechol amines which normally form might be deficient; conversely, excess phenylalanine metabolites have been shown by Bessman & Tada (23) to interfere with the metabolism of indole compounds. All components of the reaction are present except a specific enzyme in the liver, so this particular disease of the nervous system turns out

to be strictly one of liver metabolism. So far, the disease can be controlled if the infant is put on a phenylalanine-low diet within the first few months of life; in time, perhaps, replacement rather than withholding maneuvers will become possible.

Insufficiency of vitamin $B_6$ is associated with seizure states. Pyridoxine has been found effective in treating infantile convulsions (48), and will promptly relieve seizures induced in man or animals by lack of pyridoxal due to either $B_6$ dietary insufficiency or interference with the action of the pyridoxine kinase (or binding of pyridoxal phosphate) by such antimetabolites as methoxypyridoxine (75) or toxopyrimidine (251), or by the convulsant thiosemicarbazides (230). Pyridoxal phosphate, in turn, is the coenzyme for the decarboxylase that, among other reactions, forms gamma amino butyric acid (GABA) from glutamic acid; so a sufficient decrease in this leads to decreased GABA. This amino acid, in its turn, may be related to inhibition (Sokoloff), and does alter dendritic potentials [e.g. of Purkinje cells, according to Grundfest and Adey *et al.* (4)] and neuron thresholds. Thus a clear sequence exists from several convulsant conditions through decreased pyridoxal-P, GABA, membrane potential, neuron threshold, to actual spike discharges (158).

Unfortunately, there is other evidence dissociating the convulsant action of these drugs from changes in brain concentration of pyridoxal-P or GABA [e.g. Rosen *et al.* (251), Terzuolo *et al.* (277)]; so the issue remains clouded. Indeed, the common story of relating chemical actions to functional effects has been one of early simplicity and later doubt. The role of acetylcholine in neural function, still uncertain (95, 100, 103, 215) more than a decade after the introduction of diisopropylfluorophosphate, supposed to be a specific inhibitor, but not fully so (34), is a case in point. A further example is the evidence for low ATP [and CrP and membrane potential and threshold (150)] as an alternate to GABA as a basis for convulsions. In a strain of mice susceptible to audiogenic seizures, a defect in adeninetriphosphatase appeared just during the seizure-prone period (1). And, of course, pyridoxine is involved in many other reactions besides GABA formation, including even those involving the catechol amines and indoles.

In the widespread disease or diseases known as schizophrenia, the picture is far less clear; but there is growing evidence that here also metabolic errors may dominate the picture. A strong hereditary factor has been demonstrated (154, 155; but see 146). This might act through a disturbance in phosphate metabolism, for evidence is now converging on a general cellular error in the handling of organic phosphates, seen especially in nucleotides of red blood corpuscles (28, 123, 124, 223; Ling, N. S. & Gerard, manuscript in preparation). Other biochemical and physiological abnormalities have been described in schizophrenia by Richter (244), Kruse (164), Folch-Pi (74), Cole & Gerard (47), in which see especially the chapter by Domino, McGeer & McGeer (205) and Rubin (255), but most of these are still moot in the view of Kety (157); and, in any event, such a discussion is beyond the scope of this chapter.

## STRUCTURAL ORGANIZATION

### *Topography and Topology*

The more than 10 billion neurons in the brain are not distributed uniformly in space nor connected with one another to form random networks. To some extent, perhaps a large one, the location of gray and white and the positioning of neuron clusters is an accident of the evolutionary process. If the primitive neuraxis had additional coordinating neurons superposed at the front end, with express pathways to connect these with more caudal parts of the body, it is understandable why the gray is on the outside of the hemispheres and the white on the outside of the spinal cord. With various distance receptors appropriately gathered at the front end of the body, after bilateral symmetry and an anteroposterior gradient established a front end, then the special neuron accumulations for transmitting the increased information and later for integrating it would also be clustered as special bumps and nuclei near one another in the head.

But the actual architecture may well influence functioning by its geometry or topography as well as by its topology; in fact, it almost certainly does. We are told that the cortex is convoluted to gain additional surface for the expanding neuron population. But if the extra neurons were accommodated by thickening the layer of cortex, rather than by extending it, there would be no need for infolding. Nor is it likely that the folding is related to a need for proximity between pial vessels and neurons—plenty of highly active neural masses are reached by penetrating vessels. Moreover, other neural aggregates increase as three-dimensional masses with high inner connectivity. Rather, it seems that effective functioning demands that the cortical neurons

be disposed in certain geometrical relationships, with only so many layers of cells and certain distances of separation; with lateral positioning as well as depth positioning playing an important role in function (cf. Chang, Jasper, Bartley and Rose & Mountcastle). Indeed, some sort of linear folding is seen in a number of deep gray structures.

Geometry has nothing to do with connectivity as such; neuron A could connect with neuron B at any distance of separation within the nervous system and so preserve the topological network for the flow of nerve impulses (201). Only what connections exist, and their algebraic signs, matter in a 'graph' structure (131) or a sociometric one (218). The actual geometry would influence the time taken for impulses to pass between centers and so the temporal pattern of arrival of impulses of mixed ancestry. It would influence the number of connections to the extent that axon collaterals or dendrite branches vary, even on a statistical average, with distance from a cell body. And it would influence the chemical and electrical fields set up around active neurons and the spread of such fields to other units, for example by means of transmitters (von Euler). It is also, needless to say, essential to direct experimental manipulation of the brain.

The spread of activity waves and patterns through a neuron mass is thus probably highly dependent on the actual topographic relations, as is the passage of light through plane or curved glass. Some kind of focusing is indicated both by observation (179) and theory (24), as will be discussed. A prototype is perhaps to be seen in the experiment of compressing a frog sartorius with a slightly tilted plane: conduction remains intact when approaching from the wide to the narrow portion of the compressed region, is blocked in the other direction (82). If, in the course of evolution, neurons have tended to migrate towards one another, centralization, and towards the head end of the animal, cephalization, this presumably has functional value and also indicates that topology is not enough.

### *Table of Organization*

DECISION POINTS. Topology is, however, of the utmost importance. Neurons are not randomly connected throughout the nervous system; there are major and minor flow channels in the grouped fiber tracts, as well as free seepage in the neuropil masses. An enormous amount of detailed mapping has been done, but very few general principles have yet emerged. Synapses, as compared to unbroken fibers, are notoriously poor in transmitting information. They are slow, nonquantized and variable, and the information input and output are loosely linked. In the nerve fiber, transmission is speedy, constant and dependable, and there is normally a 1:1 relationship between input and output. Yet, although a single cell body can maintain an enormously long nerve fiber, most cell processes are short, and the conducting channels are chopped to bits with synaptic intersections and interpolations. They may even conduct, by electrotonic currents, in a graded fashion and with a decrement (36). Clearly, the gain in mixing different sorts of information, in modifying current activity by past residues, in modulating functional state in accord with wider body conditions, as chemical milieu, and in integrating all these influences into a single output pattern, is of far greater value to the organism than are speed and precision of transmission, as such. The synapse, or more broadly the total pre- and postjunctional synaptic mechanism, is the essential decision point in the nervous system; and the number of synapses and their patterns of interconnection are perhaps the most important parameters of a nervous system. In no case are these known or even seriously guessed at.

FEED-BACK LOOPS. Some components of the connectivity patterns are now recognized. Perhaps most important is the feed-back loop, nearly always a type of automatic volume control. At practically each junction along a pathway, from receptor end organ to effector element, including the synaptic links en route, there is a negative feed-back control from points downstream (Livingston, Neff, Paillard and French). French, for example, specifies the existence of feed-back control of ear, eye, olfactory bulb, muscle spindles, skin, and sensory relay functions in cord and brain stem, by cerebellar and cerebral action on afferents, as well as of temperature regulation, endocrine secretion, sensory gating, awareness level, motor performance, etc. Adrian notes that even the secondary controls on receptors feed information back to the nervous system. This negative control is essential if explosive irradiation is to be prevented, as will appear; but it is not immediately clear why these controls are so numerous—a single regulator at the input would suffice for the most obvious control need. If, however, perceptions are built, like motor acts, of learned components, and higher level keyboards play upon lower level ones (Paillard), clearly such multiple control is called

for. Moreover, input and output are not symmetrical in the nervous system, if only because of the great convergence present, so feed-back loops might have different functions at various stages. Presumably some control of volume and some gating of time must be applied to every rivulet of information flow as well as to the great through rivers.

Moreover, this is true for the complex learned behaviors no less than for the simple ones, e.g. eye tracking (Whittridge), lens accommodation (Fry) and cerebellar control (Paillard). Speech is monitored by aural feed-back, and a delay in this of one phoneme (about .05 sec.) can play havoc with thinking as well as speaking (Zangwill). The question of positive feed-back loops certainly needs far more study. These are probably involved in attention and vigilance (Bremer). [Warming the hypothalamus decreases reticular arousal of the cortex (Ström). Reticular formation stimulation can increase the cortical response to light (French) or to thalamic stimulation (Livingston); and a positive feed-back via epinephrine liberation is seen for the reticular formation (Ingram) and for receptors (Gray), including muscle spindles.] But little fact is available here. Even more theoretical is the involvement of both positive and negative feed-back loops in relation to learning. They should be involved, as will be seen, in the progressive channelization of impulses in the useful neuron path and the elimination of useless irradiation to others.

FLOW PATHS. Still more generally, the over-all table of organization of synaptic patterns must account for the inward flow of information and the outward flow of decisions. What are the channel capacities needed? What are tolerable and optimal signal-to-noise ratios? What redundancy of information and equivalence of channels is optimal? What is the balance between series and parallel channels? What are the factors of convergence and of divergence at various decision points? Above all, what is the command hierarchy? What fraction and what kinds of decisions can be handled at the local, peripheral level; which must be relayed on to a more central command center; which ones must run the full chain to the topmost centers? And where are these? —gathered together in the cortex or centrencephalon (Penfield) or even in the reticular formation [see Jasper *et al.* (149)], or widely scattered; anatomically constant or shifting with conditions, so that the 'best-informed' the appropriately activated neurons take command in each case? [Livingston, and Ashby (13) carry this discussion further.]

The same questions of efficient handling of 'intelligence' and 'command' face an army, a university, all operating institutions, and organisms and cells. The optimal flow pattern varies with the size of the organization, required speed of response, types of input and many other factors. Students of the brain can probably obtain valuable cues from the analysis of organizations (191) and from the theory of computers (9, 22), themselves relatively simple organizations. Eventually, when the answers learned by the nervous system in the course of organic evolution are revealed, they will probably repay workers in the other fields with fresh insights. How these patterns are laid down in the nervous system is a separate problem, to be considered later.

### *Cell Types and Specificity*

STRUCTURAL CONSIDERATIONS. Besides the quantitative differences in connections and locus just considered, neurons differ in kind. Subordinate to the major dichotomy of cells in the nervous system between neurons and glia (and there is not yet clear evidence that glia cells do or do not conduct impulses; they contain pseudocholinesterase rather than true cholinesterase according to Tower; but this is also moot, especially in invertebrates), there are such important secondary dichotomies as between neurocrine neurons, central receptor neurons, central autonomic neurons, long and short axon neurons, and many more. In general, like neurons tend to be clumped together; at least different anatomical regions often possess cells with distinctive composition and appearance, are differentially sensitive to, even destroyed by, different substances, occupy a regular position on some quantitative scale, as metabolic rate or glutamic acid concentration (Tower; 88, 129, 139, 273), or differ in their physiological properties, such as ease of initiating and of maintaining repetitive discharges. A characteristic amino acid chromatogram constitutes a 'fingerprint' of each part of the nervous system (248). Synapses differ fantastically in their detailed morphology, a likely guide to differences in functional properties and mechanisms (82). They differ in raising or lowering the excitation level, or the threshold (excitatory and inhibitory synapses); they operate with a factor of safety of less or of more than one, and thus do or do not require some summative action to be effective (98, 186); and they invest different neurons to different extents and in differently patterned loci (Chang). Fiber types, different in structure, chemistry, timing, electrical patterns and physiological

properties are well known [see for example temperature block (Zotterman), sensitivity to glucose lack (Hillarp), physiological specificity (Lloyd) and chemical specificity (Ingram, Ortmann)]. Age differences are striking (260, 288).

CHEMICAL CONSIDERATIONS. Most striking differences are in the neurons themselves, in size, structure, composition and metabolism, and physiological properties. Details are scant on the functional side, largely uninterpreted on the morphological one. The clearest evidence is probably at the chemical level, since different regions are differentially and fairly specifically destroyed by different lacks (Brožek) or additions. Ingram adds the case of goldthioglucose, which destroys the ventromedial thalamic nuclei, to many others that have been gathered (86, 91, 119). Poliomyelitis virus attacks anterior horn cells primarily, streptomycin or thiamin lack hits the vestibular nucleus. Carbon disulphide dissects out the caudate nucleus, alcohol demyelinates the mammillary bodies, carbon dioxide acts on the striatum, hypoglycemia fires the amygdala, and low oxygen blocks the globus pallidus. Various vitamin deficiencies initiate degenerations in different portions of the nervous system, even in different portions of a neuron. Dendrites are rich in enzymes and poor in Nissl substance compared to perikarya, and myelin on axons in peripheral nerve (lipid) differs from that in central axons (lipoprotein) (Tower). Autonomic centers are resistant to oxygen and sugar lack, and rich in catechol amines. Aldosterone secretion activator is concentrated in the posterior diencephalon (69); specific neurosecretory regions exist (Ortmann); and different neurons are specifically sensitive to changes in blood temperatures, salts, sugar, gases and hormones (Harris). The reticular formation is easily depressed by hypnotics, and different regions in it are specifically sensitive to the epinephrines or acetylcholine (French); and so on and on. Since the basic metabolic processes are alike, in liver and muscle and brain cells, these differences are remarkable and presumably of functional importance.

With microtechniques for studying potentials and discharges of single cells and for applying drugs directly to them [e.g. Curtis & Watkins (53)], there is increasing evidence for different pharmacological sensitivities of various cells and even cell parts. Single receptor cells of insects respond differentially to different concentrations of sugar and of salt (Pfaffman), and a retinal receptor can discharge different impulse trains to different colors (125). Only Renshaw cells are known to respond to acetylcholine, many others clearly do not [but see Marrazzi (193)]; and various cord or cortex cells, motor or interneurons, respond differently to GABA and to other amino acids. Strychnine affects potentials of a given cerebellar neuron as produced by impulses over some paths but not others (234), and influences other cells not at all (173). Inhibition in mammalian neurons seems to be associated with an increased membrane conductance to $Cl^-$ (70), while in crustacean cells the conductance change involves rather $K^+$ (64). Cord and cortical neurons, and apical and basal dendrites, differ in the locus and kinds of mitochondria and in physiological properties [see Roberts (248)]. In general there is ample evidence that various membrane sites, and internal regions, can differ from cell to cell and from place to place in one cell—even with age for a given cell type—as to structure, composition, and drug and other chemical sensitivity, and as to permeability, potential, ion gating and other physiologically important properties (Grundfest, Tasaki).

Such chemical specificities are important in allowing generalized messages from the organism to affect the nervous system differentially. Here lie the links between chemical and neural homeostatic mechanisms, engaging the nervous system by displacement of the body's physiological constants, as well as by such special endocrine responses as the adrenal steroids and catechols released in stress, the thyroid hormone increase with low temperature, and the gonadal products that trigger behavior. By such chemically receptive neurons the basic biological drives become converted into patterns of appropriate behavior. An interesting suggestion (Pribram, Stellar) relates the highly branched and large-surfaced neurons of the visceral nervous system, and the rich vascularization of these centers, to their sensitiveness to transported signals. Moreover, slow and prolonged potential changes are evoked in them by blood changes (Ström, French).

The anesthetics seem to depress generally and their differential effects depend on quantitative gradients in the nervous system. The more subtle psychoactive agents must depend more on qualitative differences, as must certain regional disorders as the lenticular degeneration of Wilson's disease or the combined cord degeneration of pernicious anemia. As already indicated, it seems a reasonable hope that functional subsystems of the nervous system are at least somewhat specific chemically, and that the neurotropic and psychotropic drugs will be able to reveal them by a type of chemical rather than of anatomical dissection [e.g. Olds (221–223)].

FUNCTIONAL CONSIDERATIONS. Whatever the specific attributes of neuron populations may be, other than those imbedded in a fixed structure, they can affect function only by influencing the physiological properties at the neuronal and the synaptic levels. Changes in neuron thresholds and in their spontaneous fluctuations can dominate the decision as to discharge or no discharge of the neuron; and this is largely determined by the potential picture, across and along the membrane. The membrane state, including that of transmitter or receptor regions, also contributes to the effectiveness of transmission across a junction and to the ease of fixation—the leaving of an enduring change—as a result of such junctional activity. There is reason to believe that most conditions altering the neural machine do not act on the nerve fibers primarily; these are ordinarily little affected as compared with the perikarya and the synaptic portions of the mechanisms. Only as neurons alter their firing patterns and as synapses pass or stop the impulses reaching them is immediate behavior affected; and only as the places of such activity are altered is subsequent behavior changed. Perhaps subjective experience can arise from changes in potential fields and metabolic processes involving cells, aside from the flow of impulses; but the answer is at present beyond us.

*Organelles and Function*

The organelles of neurons serve the same basic functions as those of other cells and, far from bags of enzymes, are highly organized for their particular functions—as are neurons in their nets and masses. The genes and chromosomes are there to carry ancestral wisdom, the nuclear and surface membranes to bound molecular space, the mitochondria to control energy flow, and the microsomal particles to preside over synthetic processes. But special conditions and functions obtain for these in neurons, and there are even special structures present (Abood). Nucleoli are solid protein and oversize (Tower)—related to the rapid protein synthesis by neurons. The vesicles at prejunctional endings may contain transmitter molecules and the discharge of these has been related to physiological properties, especially at the end plate (Fatt). [In some situations vesicles are postjunctional (281), which seems to raise doubts.] Some particulate materials are practically pure secretion granules (von Euler, Ortmann, Hillarp). Membranes have highly specialized sites, usually regularly and finely folded, at which chemical alterations are transduced into potentials, largely by electron shifts at the intramolecular level (Fatt, Wald). The thousand-layered zone of retinal rods, acting like a photomultiplier tube, and the similarly piled-up end plates or electroplaques (Grundfest), making a voltaic pile, demonstrate the rich organizational resources of protoplasm, as its synthetic and accumulative ability is shown by the 40 per cent concentration of visual pigment in rods, the solid protein nucleoli, and the nearly pure catechol amine granules in orthosympathetic neurons or their derivatives.

Related to special receptor sites, some neuron regions seem adapted to maintain a relatively steady potential level of variable magnitude, as in certain dendrites; other regions depolarize explosively and, after an all-or-none propagation, regain the initial level. Thus, within a single neuron, there is a clear separation of information storage and information transmission. Finally, different membrane regions are differentially sensitive to particular molecules, to different ion concentrations and ratios, to the rate of energy flow and creatine phosphate concentration, etc., as already noted.

*Molecules and Memory*

Not only are neurons specialized for short-term handling of information, they are also involved in long-term storage. Whatever the locus and mechanism of such engram formation, the trace must involve patterned changes of molecular arrangements in organelles or of atoms in molecules, or both. The number of bits held in memory strongly suggests the involvement of protein or nuclein molecules, since only polymers of such multiple units are sufficiently rich in patterns to hold all the information. It still remains, however, to demonstrate that experience, carried in nerve impulse trains and cell potentials, can alter the character of these molecules. [The 'specification' of an innervating nerve fiber to fit the newly innervated muscle, noted by Sperry (268), perhaps comes close to this.[2]] A reasonable transducing and storage mechanism has yet to be

[2] Work recently reported by Morrell (213) promises a definite answer regarding the quantitative involvement of RNA in storing experience. If some cortex area is made ictal with alumina cream, the equivalent crossed area, if supplied by both callosal (specific) and deep (nonspecific) connections for a week, will develop a low threshold and become ictal. It then fires, even when isolated as a slab, both spontaneously and when triggered by activity in adjoining cortex. Neurons in

suggested. The steady turnover of neuron protoplasm, up to several times daily, may be related to such learning ability. The outsize nucleus, the presence of large and variable amounts of ribonucleic acid (RNA) in the cytoplasm, contributing to the Nissl substance, the fast peripheral flow of enzymes and protoplasm, and the high metabolism of neural somata are all related to an unusually rapid rate of synthesis of polynucleotides and proteins.

If so, one can vaguely imagine that the flow of impulses and electric fields could, like frequency modulation, alter the order and frequency of laying down of nucleotide and amino acid moieties and so control their pattern in the molecular tape that is formed (145), or the configuration of the entire molecule (Yuwiler, A., personal communication). How such a coded molecular tape would, in turn, control the synaptic and other properties of a neuron so that impulses will enter and leave it in appropriate relationships has not been faced, nor even tied to the changes seen in microsomes (Abood; 79), end knobs or apical dendrites (Galambos & Morgan; 260) on activation. The close relation between outer membrane, endoplasmic reticulum and other cytoplasmic particulates may contain clues to the answer. Nor has the problem of long-enduring memories, far beyond the presumptive life of any particular molecular inhabitant of a neuron, been effectively handled (286). Indeed, the apparent storage of learned behavior patterns in the essentially nonneural tail of a planarian, which is able to regenerate a new head so that the re-formed animal performs as well as an intact trained one (198–200), almost demands molecular templates and raises profound problems as to the manner and locus of storage. (Learning processes and mechanisms are considered further in a later section.)

## DYNAMIC ORGANIZATION

### *Neuron Properties*

THRESHOLD AND EXCITATION. The neuron is the integrating element of the nervous system. It receives multiple messages via its synaptic scale, is influenced by the physical and chemical surround, and is modified by its own past experience; and to all these it equates an output which may be as simple as a single discharge-no discharge or as complex as an impulse train with wide variance in the number and timing of pulses—or even as two simultaneous trains differing in pattern in two axons of a single cell body (36). A unit fires when the excitation state at an appropriate locus, presumably the proximal axon segment (Eccles, Frank), exceeds threshold. Excitation is ordinarily associated with brief and transient changes, mainly induced by synaptic activity and occurring as more or less quantized increments that add in time and space. Threshold is ordinarily a maintained state, involving a slowly reversible or essentially irreversible shift in properties.

Between the extreme cases of, say, a single suprathreshold presynaptic impulse, on the one hand, and a threshold level maintained by the intra- and extracellular potassium ratio, and the attendant membrane potential, on the other, there are probably all possible gradations. Nevertheless, it makes for clarity to keep the distinction sharp and to examine separately the control of threshold and the control of excitation. It also seems useful to recognize the shorter and the more enduring threshold shifts. A shift in dendrite potential, induced by excitatory or inhibitory terminals, constitutes a short threshold change more than an actual excitation change (Bartley). Thresholds are concerned primarily with the storage of information, temporary or enduring; excitation, with its transmission.

THRESHOLD CONTROL. The axon segment will fire when its membrane potential falls to a critical level; as the pre-existing level is low or high, so is the threshold. Both the maintained level and the quick displacement of it can be influenced by surrounding chemicals, by direct current potentials and the associated steady currents, and by nerve impulses with the accompanying synaptic potentials and eddy currents. An instructive example of the interaction of chemicals and impulses on neuron thresholds is afforded by the exaggerated sex behavior induced by pyriform lesions when sex hormones are present, not in their absence (Gloor). A high external potassium-to-calcium ratio can lower the axon segment membrane potential so as to give repeated firing, but this is unlikely in the range of normal variation. Sufficient impulse bombardment of an apical dendrite can produce the explosive increase in membrane permeability of an active response, and the resulting eddy current may fire the axon; but present evidence indicates that this is the exception rather than the rule (Eccles, French). Ordinarily the threshold of

such a locus, 'remembering' their over-activation, seemed, in preliminary observations, to have accumulated RNA under the perikaryon membrane. Further, Kreps (163) is reported to have shown an altered RNA turnover on conditioning.

the axon segment is controlled by the chemical field bathing it and by polarization currents reaching it, mainly, from other portions of the soma and dendrites. These currents depend on the chemical environment of dendrites (and soma) [e.g. (120)], on external currents that flow through them, on membrane conductance, and on local potential differences along the neuron surface, mainly produced by incoming impulses which constitute briefly enduring sources or sinks for electrotonic currents that involve the axon [Chang; Bishop (27)]. A final point: it is usually assumed that, left to itself, the neuron threshold is high enough to ensure inactivity, but the converse may well be possible. Many neurons do show rhythmic spontaneous activity under physiologic conditions. Brain damage, including developmental abnormality (Hicks), is commonly associated with convulsive or other overactivity. Learning, at the motor or social level alike, involves differential inhibition. Sleep rather than alertness is the equilibrium state. Causalgic and related pains involve a decreased somesthetic input (184). Inhibitory recurrents from motor neurons seem important. High cord-section or anesthesia increases the responses in spinal afferent tracts produced by a given dorsal root stimulus (Livingston), while stimulating several limbic or cortical structures decreases cord responses (French). Blocking the presumptive inhibitory transmitter, GABA or factor I, as by strychnine (Grundfest), gives generalized discharges to minimal stimuli. A steady outflow of impulses keeps the external sphincter of the bladder closed; these are inhibited during micturition (Ruch). Perhaps neuron thresholds are kept up by a continued rain of inhibitory impulses.

DENDRITIC (SOMATIC) POTENTIAL. The threshold of the neuron, then, is primarily controlled over the long run by chemicals in the intercellular fluid and currents passing through it, over the short run by impulses reaching the neuron far from the axon hillock and summing spatially and temporally to give the dendritic or somatic potential.[3] Excitation, in contrast to threshold control, depends primarily on impulses reaching the axonal pole of the neuron and acting with little spatial summation and with even less, perhaps no, temporal summation.

The slow, cumulated, nonpropagated dendrite potential, like a generator potential (Bartley, Chang, Eccles, Gray, O'Leary & Goldring), is an ideal integrating and storage mechanism. Impulses reaching any part of the dendrite-soma system could sum algebraically and pool their electrotonic influences on the axon. Further, over a longer range, changes in responsiveness of these neuron parts to impinging impulses, or to ambient conditions, afford a simple link between past experience and current activity. Not only in the cerebral cortex, where steady potential changes parallel activity in projection areas (176), spreading depression waves and the more complex behavioral states (O'Leary & Goldring; 179), and in the cerebellum, where polarization alters tonic activity (Brookhart), but also in older and simpler structures, potentials parallel state on a lasting basis [e.g. with temperature or carbon dioxide (Ström)]. The single cell layer of the hippocampus shows marked potential shift with seizures (Green), or amygdalar tetanization (Gloor). Amygdala potentials build easily (Gloor), and enduring seizure discharges result from short stimulation (8); and, in the frog telencephalon, the steady potential and waves of activity are closely related (175).

Ultimately, of course, the membrane and related changes reduce to physical chemistry (Peters). Eccles relates hyperpolarization, by inhibitory synapses and presumably that following axon discharge, to a relative increase in permeability to $K^+$ and $Cl^-$ of the dendrite membrane. For end-plate activation, Fatt sees no ion flow across the membrane but electron shift along enzyme molecules palisaded in the receptor site. Gray boldly relates the Weber-Fechner law to the ion ratio across relevant membranes.

Whether at special electroactive receptor sites in the membrane, in the palisaded layers of molecules in the membrane at large, or involving the ion and molecule flow within the cell as controlled by interior organelles, the neuron threshold depends on chemical architecture. The frequency and magnitude of waves of spontaneous threshold change are dependent on cell metabolism, probably acting through an ionic

[3] The concept of an integrating somatic potential, underlying facilitation and inhibition, arose from reading Sherrington's paper on central excitatory and inhibitory states and was accepted by him in a discussion in 1927 (108). The idea was published in 1932 (83, p. 547). It was supported experimentally and further developed theoretically in the late thirties and early forties by Libet and Gerard (118, 174, 175). The suggestion that inhibition and excitation might depend on the position of synapses, near the dendritic or axonic pole of the somatic potential, was made at this time (89). After years of dormancy, this work helped trigger extensive studies of dendrite potentials that have redirected thought in recent years [O'Leary & Goldring, Bartley; see also Bishop (27), Bremer (29) and O'Leary (225)].

trip mechanism (174). The more random threshold fluctuations may, like those at the end plate, represent the chance release of presynaptic transmitter packets; but the presence of comparable random fluctuations in the threshold of nerve fibers, where such packets are not involved, leaves the question open.

If 'pure' inhibition be restricted to hyperpolarization of the synaptic region of the postsynaptic membrane, presumably by an inhibitory transmitter (128), then many other types of central inhibition exist. Not only can exciting impulses be cut off from the goal neuron by inhibitory inputs, but also the effectiveness of such impulses might be altered by changes in presynaptic terminals (with less transmitter release on activation, for example) or in the postsynaptic membrane outside of the receptor site. A more stable membrane or one with greater conductance would decrease electrotonic spread from the activation site in the dendrite to the axon segment which might fail to receive the minimal current needed to excite it (63, 64). Whether GABA, or substance I [or even the epinephrine group—or histamine, e.g. (194)], is a true inhibitory transmitter or is a 'modulator' acting in this fashion is in active debate [see Roberts (247)].

Still other types of 'inhibition' relate to the rebound hyperpolarization seen after repetitive activation (276), or to an excessive depolarization that precludes spike propagation. [Compare this with striated muscle, which Jenerick & Gerard (150) found to give only local responses when depolarized to a fixed level, and with the action of methonium at the motor end plate shown by Paton (229).] Some nerve fibers can either inhibit or excite a given muscle or nerve cell (276, 293), depending on local conditions at the junction [cf. Hagbarth & Fex (130)].

In any event, the qualitative differences in neurons, the existence of excitatory and inhibitory connections, the differential sensitivity to drugs of different neurons and different parts of a neuron, the presence of specific receptor elements within the nervous system with highly developed individual chemical sensitivities, and the generally greater richness possible when a qualitative particularization is added to an indiscriminate quantitation, all indicate the importance and ubiquity of chemical factors in maintaining and manipulating neuron thresholds.

JUNCTION PROPERTIES. It is often difficult to assign specific aspects of the synaptic mechanism to the actual junction. Changes in presynaptic spikes and eddy currents or in transmitter store and release, as well as threshold changes in the postsynaptic cell body and its processes, and in the spatial interaction of many junctions, all can contribute to the success or failure of a message in crossing a given synapse. Spatial summation and after-discharge effects may well be postsynaptic; temporal summation and more delayed time changes are at least restricted to the particular incoming pathway—witness the posttetanic potentiation effects. Further, the enduring changes of activity or inactivity presumably involve the junctional region, but the evidence on this is not decisive. Moreover, the vigorous movements of the processes of living neurons, as well as the active chemical turnover in these cells, raise problems regarding specific information storage that are not easily answered. The extent to which the modulation of channel transmissivity depends on the junction is also uncertain. Feed-back controls on transmission, chemical alteration of thresholds, and steady or transient potential fields and currents probably act on the postsynaptic elements rather than upstream to them.

### *Interaction Patterns*

The nervous system uses an alphabetic rather than an idiographic language. Large numbers of units of relatively few kinds are combined in different patterns to give particularized meanings and behaviors. Three sorts of mechanisms of interaction can usefully be distinguished: particular synaptic networks (51, 52, 133, 201, 203, 204, 212), chemical and electrical fields (97; Fessard, O'Leary & Goldring), and, a combination of the above, certain statistical properties of large cell aggregates or masses (7, 24, 239, 240). Beyond these general relations are the various particular ones depending on the major neural structural and functional systems.

Field mechanisms lend themselves to synchronization of action of masses of neurons and to mass effects in general. Nerve nets and assemblies lend themselves to specific activity patterns and to reverberation. Both mechanisms, generalized to statistical aggregates, can produce slowly moving waves (71, 118, 179). It is worth noting that reverberation and patterned activity in general demand successive, and therefore nonsynchronous, activity of separate neurons, whereas field effects and synchrony demand the simultaneous activity of masses of neurons. Certainly a given neuron cannot successfully interact with its fellows both simultaneously and sequentially, except during successive time periods. It is even worth considering that certain neurons may normally be involved via the one mechanism, others via the second.

The nerve fiber is essentially all-or-none or digital and, although modifiable over a moderate range, it delivers quanta of excitation at a synaptic ending. The nerve cell, and probably its short processes, in contrast, is essentially continuous or analogical in its properties, and can show great and graded changes in its metabolism, membrane potential, threshold, somatic potential and the like (98). A time modulation is important; further, the spontaneous rhythm that obtains for many, if not most, neurons may contribute to the time sense and to the discontinuity of experience. Not only does the size of an evoked visual potential of the occipital cortex depend on the phase of the alpha rhythm at which it arrives (Bartley), a similar fluctuation in reaction time has also been related to the phase of the alpha rhythm at which it is measured (17, 180). Moreover, experience seems to advance in a series of time frames, of about a tenth of a second in man, much as do moving pictures (206, 272). And spontaneous rhythmic beats of single neurons, as well as circuits between cortex and diencephalon, are involved in the rhythms of the mammalian cortex [but see Burns (39)] as well as of the amphibian telencephalon (87, 174).

FIELDS. The field effects can be general, depending on the over-all chemical environment as determined by blood and intercellular fluid exchange, or by widely separated sources and sinks of polarizing currents; or they may be localized, depending on the diffusion of metabolites and flow of currents between active and inactive neurons or small neuron groups. The vasodilation restricted to active neural regions (85; Kety) is an example of such a local effect, and the relation of activity to polarization, which in one direction increases and in the other decreases spontaneous rhythms and actual discharges, has been extensively demonstrated (39, 60, 71, 256; O'Leary & Goldring). Activity, in turn, alters the steady potential (10, 176). Intercellular currents undoubtedly also contribute to the synchronization of cell masses, most directly shown in *Vitella* (6, 72, 138) and in the frog brain (175), and probably to the spread of inhibitory waves (38, 167, 168, 283) and to the physiological state in general, including dendrite potentials (39). (Ström cites steady potentials generated by blood changes temperature in the supraoptic nucleus, carbon dioxide in the medulla that alter the EEG, muscle tension and pituitary activity, or otherwise modulate the level of physiological readiness.)

Such field or mass actions allow great freedom as to the actual neural units entering into a functioning system. The outcome can depend on the topography of the steady potential field rather than on the specific neurons that are active, just as cells in a cut flatworm regenerate in terms of their position on a metabolic gradient rather than in prespecified directions. Mass effects also come closer to making understandable the unitary whole of consciousness and behavior than does a picture of innumerable impulses racing along their separate nerve pathways. Yet this necessarily sacrifices information and some experimental evidence presents problems to field interpretation (268).

Synchrony and hypersynchrony of neuron masses can also well explain the phenomena of causalgia and other types of 'physiological inflammation' (101) associated with a continued excess of one modality of input, and a deficiency in other modalities (but see Sweet). Similar mechanisms may well underlie the build-up of convulsive discharges, motion sickness, the sex climax, certain neuroses and even the hallucinatory experiences of sensory deprivation.

NETS. Whereas field effects tend to be general and graded, synaptic action and nerve nets tend to be specifically patterned and quantized. As will be seen, the mechanisms grade into one another for large groups of neurons, in sheets or masses; yet the field and net machines are essentially polar to each other. The influence of incoming impulses on a neuron is determined by simple parameters of the synapses. Endings from one or several fibers can differ in number or intensity (two endings close together would be the equivalent of a single doubly strong one), locus (two like endings far apart may not sum their effects or may even have opposed effects on the cell activity), timing (altered frequencies or phases of incoming impulse trains can change responses from positive to zero to negative ones), and kind (where excitation and inhibition depend on qualitative differences in terminals rather than on their position on the cell body, or on comparable differentials).

Impulses tend to flow forward, from input to output, in a neuron chain or net, but they also reverberate to an important extent within closed loops or assemblies. Simple feed-back loops can give the normalization of perception and of action, already described, and afford the underlying mechanisms proposed for purposeful or servomechanistic behavior (202). They also would give the needed freedom in time, so that the response is not necessarily linked immediately to the stimulus (94, 97), and offer a mechanism whereby classes or universals can be generated from a succes-

sion of particular individual instances (232). Reverberation is also probably related to the storing of particular experiences, and perhaps to perception, to anxiety and to consciousness itself, as will appear later.

SHEETS AND MASSES. It will be convenient to defer full consideration of sheets and masses of neurons, especially since a specific model has been worked out in this case (24). Several contributors to the *Handbook* have touched on this topic (Pribram; see also 71); others have reviewed segments of neurophysiological knowledge which fit admirably into such a formal model.

When large numbers of elements are involved, provided they enter into activity as individuals rather than in predetermined large groups, then small discontinuities become smoothed into large continuities. Whether neurons are subjected to a continuously increasing concentration of intercellular potassium or to an increasingly heavy barrage of nerve impulses, they can alike show a graded change in state. Actually, the potassium concentration also changes discontinuously, at least by one ion, but the large numbers swamp out such small quanta. Under both field and net conditions, then, the statistical distributions of neuron properties become of prime importance. It will obviously be of help both in understanding and in characterizing the actions of varied neuron populations, to know the distribution of thresholds of the units in a large population; whether they follow a Gaussian curve [which explains the stimulus-response magnitudes in a spinal reflex, in the view of Rosenblueth *et al.* (253)], or whether a Poisson distribution is involved (as in the excitation of photoreceptors by quanta, as shown by Hartline), or whether still other distribution curves obtain [the assumption of an exponential distribution of synaptic delays in series parallel chains accounts for the observed complex reaction times in many situations, according to Christie & Luce (43) and Rapoport (241)].

CODING. From the rain of stimuli carrying messages to receptors, external and internal, certain items are transduced into nerve impulses. At successive junctional regions throughout the nervous system, incoming and outgoing signals are discontinuous but related, and an over-all convergence and loss of information occur. The vast and redundant detail of raw experience is filtered, grouped, generalized, interpreted and used; percepts, concepts, plans and actions arise, and are shuffled into and out of attention and execution. The flow of information is highly structured and depends on the transform functions at junctions and on the interconnection patterns. These constitute the coding used by the nervous system, and the study of this is becoming intense and productive. [See also Hick (137), MacMillan (120), Luce (189) and Quastler (235).]

The possible inflow of information is in the millions of bits per second, but the amount that can be handled is only in the tens [e.g. Barlow (15)]. Problems of input overload are met everywhere and several devices are used in 'defense'—as queuing, grouping and omission (211). Rats learn a simple discrimination in 10 to 20 trials, while monkeys, with richer awareness, may require 20-fold more (135). Men, similarly, having had their attention drawn to minute variations in the coloring of marbles, may fail to sort on the basis of major color differences (19). Repeatedly, students have outperformed expert social psychologists in judging group discussions, as secretaries have surpassed psychiatrists in rating reviews, when using given rules for selecting particular information from the total offered. Sophisticated problem-solvers often become entrapped in an hypothesis more inextricably than do naive ones; the trees may blot out the woods for anyone. The real skill of the talented thinker is in discarding all irrelevancies, in 'going for the jugular of the problem.' What is omitted in perception, memory and reason is of the highest moment.

An important way of eliminating details is by grouping messages and by neglecting uniformities. Nerve impulses are rare, or absent, from most photoreceptors except with discontinuities in space or time, so much so that visual patterns disappear when retinal movements are prevented. Marked changes in frequency of discharge of ganglion cells accompany small transitions in intensity of receptor stimulation (Bartley). Edges in a visual pattern are emphasized by the reciprocal inhibition of *Limulus* ganglion cells which automatically strengthen the bright and weaken the pale areas (242). Comparable integrating effects have been studied in the frog eye (170) and are operative in other receptor organs, as ear and skin (285). Further interaction occurs throughout the nervous system. Neff has discussed the general coding of perceived attributes—intensity, pattern, quality, etc. Information is certainly carried in the spatial arrangements of active elements and in the frequencies of impulses in them; but in all probability the coding is far more subtle, and depends on intricate on-and-off activity patterns, with changes of frequency

and intervals—not unlike the Morse code of FM—as well (Neff). Filtering out sound frequencies under 1,000 cps eliminates 90 per cent of the power but only 10 per cent of the information in speech (Zangwill). Complexity also exists for spatial patterns which determine convergence and summation, reverberation and feed-back, synchrony and potential fields, and the like (Gray). Even at the simple quantitative level, synapses may reduce an input frequency of several hundred per second to an output frequency under 10 (Chang); and one input may lead to one or to two dozen discharges (Davis). The interaction of different impulse trains has been shown to alter the experienced modality (synesthesia) in temperature (Zottermann), touch and kinesthesia (Rose & Mountcastle), taste (Pfaffman), etc. A 10-$\mu$sec. time difference in the arrival of air waves at the two ears suffices to give direction to heard sound (Davis); a shift in timing of stimuli to right and left afferents can start or stop swallowing (56); impulse frequencies relate to cell discharges in the lobster cardiac ganglion (37).

As discussed, different frequencies of stimulation, or different initial states of a neuron pool, can reverse the response elicited (see also Patton & Amassian). A single neuron can similarly be excited or inhibited by different frequencies of stimulation, from other neurons (e.g. French) or receptors—even depending on previous positive or negative conditioning (148). And the number, frequency and pattern of discharges from a single neuron can be altered over wide ranges with different inputs. A single chemoreceptor unit can fire at different frequencies to different taste stimuli; and a single photoreceptor, to different colors (e.g. Neff). Two axons of a single neuron can even fire simultaneously at separate rates (36).

The ideal approach to the problem of neural coding is to obtain the output for all ranges and kinds of input, and to do this for single junctions, single neurons activated through all combinations of junctions and neuron pools receiving impulses from various groups of afferent fibers. This program is well under way for single units in many laboratories, and a promising start has been made even for whole ganglia. By autocorrelation (16) applied to postganglionic nerve trunks while preganglionic ones are stimulated at different strengths and frequencies, Casby (personal communication) has been able to identify the impulses in fibers conducting at each velocity or similar characteristic. Such data will in time reduce the behavior of neurons and neuron nets and pools to the same quantitative rigor of description and prediction as has been achieved for activation of the nerve fiber.

*Major Systems*

The properties of neuron nets and masses have been considered so far at the most general level; later, the formation of highly specific patterns will receive attention. Between these, there exist in the nervous system major systems or organization schemes, probably including many not yet recognized. The more particular nuclei and paths, which constitute the subject matter of physiological anatomy, are extensively treated in the *Handbook*. It will not be possible here to do much by way of summary. Clearly, most structures connect with most others, and often by direct paths. And, equally clearly, each author finds the neural region that has won his devotion to be responsible for great physiological deeds. The competition is especially keen between the reticular formation (French), hypothalamus (Ingram), cingulate (Kaada), hippocampus (Green), amygdala (Gloor) and the whole limbic system (MacLean). At least the amygdala facilitates and the hippocampus inhibits the hypothalamus (195); this controls pituitary hormones in a highly patterned way (143), and influences drives and vigilance (Stellar), partly via the reticular formation (French).

LOCAL AND RELAY. Perhaps the most important dichotomy, certainly the longest and best known one, is that between short-circuit and long-circuit responses. Most responses were primitively at the ganglionic or segmental levels, with minimal spread to adjacent aggregates. Later, with anatomical centralization and cephalization, there was also spread of physiological activity, involving especially long-circuiting towards the head end. Then were developed the powerful distance receptors feeding increased information to new superposed nuclei, and new unbroken nerve tracts to handle the information flow between these new centers and the main body.

The central gray columns and the fasciculi proprii, with their rich neuropil, constitute a widespread mechanism for local traffic and peripheral decisions. As pointed out earlier, a major challenge is to rationalize the nerve impulse traffic and the associated information flow. Presumably the best established, most regular and phylogenetically oldest responses can most safely be entrusted to local autonomy. This is well exemplified in the axon reflexes and the ganglionic reflexes of the autonomic nervous system, which continue with little disturbance when disconnected from the central neuraxis, and only less well in the basic spinal reflexes which, although clearly modulated from higher up, continue to function after

cord section. In contrast, situations demanding the maximum amount of experience and choice, involving multiple alternate input and output patterns, may be lost with even small lesions in the highest structures—as in the aphasias. Nevertheless, our quantitative knowledge of the actual flow of traffic through the complicated channel network is minimal; the extent to which one route can substitute for another in an emergency, what type of traffic has priority on the boulevards (like passenger cars) and what type takes the byways are questions for the future.

LOOPS. The significance of feed-back loops also has already been mentioned. At this level such questions as the following present: what factors determine the number of synaptic breaks in the direct path; the number and kind of modulating connections that play upon each of these way stations; the secondary paths that issue from each way station to modulate still other primary and secondary paths in the nervous system; the intensity and dominance order of these various flows of messages. Many of these are described in detail throughout the *Handbook* (Livingston, Whitteridge, Jasper, Gloor, Paillard, Bartley, Brookhart, Rose & Mountcastle, etc.), but the ordering or integrating questions have certainly not been answered; mostly we are not yet even asking them. Servomechanistic studies at the peripheral level made by Stark and Baker (269, 270) and Clynes (44) are a good start.

SPECIFIC AND GENERAL. A final dichotomy has been adumbrated ever since the terms reason and emotion became meaningful, and much recent research bears out the existence of two basically different neural systems related to these. A distinction between diffuse, affect-tinged, unlearned experiences, on the one hand, and particularized, rational and learned ones, on the other, was attempted in the protopathic-epicritic distinction of Head and Holmes (happily exhumed by Rose & Mountcastle, also discussed by MacLean). A similar separation was seen in fiber types, especially those serving quick and slow pain recognized by the St. Louis group (but challenged by Sweet), and was met clinically in the phenomena related to causalgia (101, 184).

Clinical and experimental studies first opposed the hypothalamus to higher centers. Later the different structures and functions of the old and the new cortex became clear, with the former (whether called the limbic system or some other name) associated with the emotional components of behavior. Still later, the extensive reticular system was recognized in its various portions as biochemically distinctive, and as controlling, through diffuse systems, the level of cortical activity and the degree of alertness or even of consciousness. It is useful to discriminate the level or intensity or set of consciousness from the content or patterns within it. The former is closely related to the medial diffuse systems and to such chemicals as the indole and catechol amines; the latter to engrams laid down by experience, presumably mainly in the cortical sheets.

The opposed aspects of neural organization, mass or molar on the one hand and particulate or micro on the other, appear in all phases of structure and function. Pavlov (and Lashley) has been pitted against Sherrington, the gestaltists against the behaviorists, adherents to field mechanisms against those favoring synaptic ones, diffuse against discrete in neural systems and behavioral patterns. Both are, of course, present and useful.

As the nervous system, during individual development, passes from massive to differentiated reflex responses (45, 142), so, during evolution, it has probably followed a like course. Coelenterates possess a neuropil-like nervous system, with generalized nonpolar synapses and with massive responses of the whole organism prominent in their behavior. Such undifferentiated structures, perhaps able to transmit symmetrically, are seen in the neuropil of the old central gray masses of the brain stem and in the short axon connecting paths and feltworks; and the corresponding responses are met in the mass reflexes of the spinal animal and the ictal discharges of the intact one, and to some extent in the intense pseudo-affective responses of diencephalic and other 'basal' preparations.

Upon raw mass properties were early superposed a differentiation of units. Neurons became structurally and chemically specialized, and developed different sets of physiological properties, considered elsewhere, which favored particular roles in the integrated functioning of the nervous system. Larger cells with longer processes and faster all-or-none conduction supplemented the smaller, shorter and slower units; and discrete action spikes become relatively more important compared to fields and gradients, to steady electrotonic potentials and to chemicals. The high speed quantized messages of axons may be a specialization from conduction by decrementing electrotonic spread which evolved earlier and perhaps still dominates in gray masses [e.g. Bullock

(36)]; indeed, even in long axons the question of a slight decrement has recently been reopened (188).

Further development yielded the older integrating structures of the reticular formation, hypothalamus and rhinencephalon, using express conduction paths, yet in a somewhat primitive fashion. Here are the diffuse systems, including cells with short processes, multiple synapses, wide connections, high chemical sensitivity, slow adaption and prolonged potential changes. These act widely and relatively [but not entirely, as shown by John & Killam (151)] nonspecifically, serving a protopathic type of affective experience and mainly setting the conditions in which the discrete systems operate. The newest cortex and its associated lemniscus tracts and way stations, the discrete systems, are concerned primarily with content rather than set and serve an epicritic type of patterned and discriminating conative experience. Yet, even here, in the cell sheets of the neocortex, field effects and mass action are important; the integration contributed by steady potential fields and the differentiation contributed by ordered nerve impulses are both needed for full function.

Diffuse systems, with their rich interneurons, able to put cell masses under barrage with repeated and recurrent showers of impulses (187), largely control the background excitation level. The old finding of Lloyd (185) that a 7 msec. delay between arrival of a pyramidal fiber volley and discharge of an anterior horn cell is shortened 10-fold on repetition, when the local interneuron pool has become active, is much to the point. Many examples are currently in attention: the gamma fiber discharges which give the motor set for alpha fiber action (Eldred) and which come from vestibule, reticulum and cerebellum (Gernandt); the auditory, visual and other modulators of receptor threshold and sensory inflow (Livingston, French); the associated feedback from receptors which also contributes to 'set' (Adrian, Galambos & Morgan, Rose & Mountcastle); the modification of cortical responses by manipulation of the reticular formation (French) or amygdala, or by thalamic impulses (Chang; 50); the similar modification of cortical steady potentials (10); the influence of nonspecific impulses to the cortex in conditioning the perception induced by specific ones (Neff); the interaction of specific and nonspecific impulses at single cortical neurons (153); the excessive suffering from pain where discrete paths are inactive (101), suffering which is relieved by leucotomy and other operations that, at least in some cases, cut into diffuse system paths (Sweet); even the control of alertness level, from sleep to vigilance, by inhibitory and facilitatory portions of the reticular formation (Jasper, Chang). The amygdala facilitates the hypothalamus and may be involved in the increased pituitary-adrenal response that accompanies psychological distress (196); activity of the amygdala increases emotional behavior in response to mild stimuli, including rage attacks and psychotic-like behavior (Gloor), but it inhibits cortical responses and ease of conditioning (Galambos & Morgan) and produces slow and perseverative thought (Gloor). Recent work (152) shows that correct learned responses to flicker are associated with matching potential frequencies in the reticular formation and cortex, interpreted as congruence between past learning and current perceptual display.

The cortical 'unit' (Chang, Patton & Amassian) is affected differently by incoming diffuse and discrete fibers (Chang, Jasper). The former act mainly on superficial layers but can depolarize apical dendrites of deep pyramids as well, giving a surface negativity. This negativity builds up locally on repetition which suggests that the 'recruitment' response is more a summation on the same elements than the addition of new ones, as the term implies. Discharge, as well as EEG waves which spindle or dome, is increased by virtue of lowered thresholds, thus making the discrete afferents more effective. The diffuse system is not without structure and can alter the spread of activity in the cortex along different paths (Jasper; compare with Pribram). That the diffuse system may also fire motor neurons is suggested by the retention of facial movements associated with strong emotion in patients unable to perform voluntary movements with the facial muscles. It also bears thought that a clear reciprocal inhibition (see later) operates between attending to content and to mood, as also between different contents and different moods.

All the old brain centers interconnect (Gloor) and interact with the new ones—a veritable metabolic pool of message flow with vast opportunities for feedback and for circular causation. Here, indeed, is 'organized complexity,' and the two great systems function smoothly together as do, in MacLean's phrase, a horse and rider. The diffuse system mainly serves drive, affect, alertness, attention—the substratum on which perception and action are carried. The discrete system deals more with the specific patterns of organism-environment transactions, with percepts and ideas, with learned manipulation especially with using symbols, as in language. The television picture comes through only when sweep

length and repetition rate, intensity and contrast are properly adjusted. Before the phonemes of speech can carry meaning, the voice pitch, loudness, speed and intonation have been set—not to mention body posture, gestures and the like. Indeed, appropriate sound filters can remove from speech either the sense [the high energy portion (Zangwill)] or the mood (fundamental frequency) while leaving the other (177, 271; Soskin, W., personal communication). Conversely, the hypothalamus, or other diffuse structures, must put emotion into speech and with some selectivity in relation to content. Feeling has only quality and intensity; thought has pattern. Feeling is uncoded, reflex and alike across species; thought is coded, learned and specific for species, culture or even individual.

There is much reason to relate schizophrenia to a disturbed interaction of the diffuse and specific systems. Beside the ability of the former to alter thresholds, and so the number of available cortical neurons (see later), it creates the set or program which guides the specific sequences of thought and action, the strategies of goal-seeking behavior [cf. Bateson *et al.* (18)]. Schizophrenic behavior is characterized by symmetrical logic (197), with a jumbling of logical and temporal elements [and perhaps by an over-all slowing of time flow, according to Lhemon & Goldstone (172), which could relate to the reduced neuron capacity]. Non-sequitors, bizarre productions, unrelated juxtapositions these are the earmarks of the illness, as the colored bits of thought and act jostle loosely in a kaleidoscope. [Compare Elkes (65) and Evarts (67).] Presumably, the ordered entry into and exit from activity of properly patterned groups of cortical neurons is disturbed. The particular moving waves, to be considered in the final section, would lose their way and move erratically in the cortex.

Time, space and logic are closely related in neural mechanisms, and they must be integrated together. And a perception, in Elkes' phrase, involves micro-reasoning. Certainly the eye responds to a static pattern, a spatial boundary between light and dark areas, and a dynamic pattern, a temporal boundary between light and dark periods, with like intensification in the frequency of impulses in optic fibers (242).

Conversely, affect has mainly intensity and positive or negative quality. Positive reinforcement is strongest in self-stimulation experiments in the amygdala or septum and hypothalamus for the rat, but in the caudate for the cat (Stellar). To the extent that these are 'sex' centers, here are 'drives,' like curiosity (134), that do not originate from disturbed internal homeostasis but rather from external relations. [When the hypothalamic-pituitary portal system is destroyed, systemic stress still evokes ACTH and TSH release, but psychic stress does not (Harris).] The relatively greater importance of external factors in drive in the more evolved organisms (Stellar) fits the high importance of 'set' in human intercommunication.

It is of considerable interest that psychologists and sociologists have come to recognize, in the functioning of groups, behaviors and roles comparable to emotion and reason. Statements in a problem-solving session by a group fall into goal-directed or socioemotional categories (14). Separate individuals or personae and separate communication channels either form amorphously or are crystallized in tables of organization in the groups and institutions studied; the 'stern father' and the 'loving mother' or 'kind uncle' appear everywhere. To facilitate flow along official channels there always exist the personal para-channels—the affable and knowledgable sergeant gets the job done while official papers sludge through channels; boards and administrators propose, executive and personal secretaries dispose. And growing behavioral science knowledge shows the need of both the rational and the affective components in proper balance for optimal functioning of the group, as for the individual. An imbalance or dissociation can result in schizophrenic-like phenomena in group as well as in individual.

## LEARNED ORGANIZATION

### *Nature*

GENES AND MATURATION. Storing information, learning from experience, involves the laying down of material patterns, of whatever sort. The particularity and quantity of learning is far too great to be accounted for except in terms of patterns or organization. Information may be in the form of specific items or of procedural rules, and the latter, including class universals, can be vastly more economical. The genes and chromosomes in a zygote cannot possibly carry the full details of information necessary to build an adult organism in conformity with the accumulated experience of the race, yet each individual forms the major neuron centers and paths and connections common to the species. The arrayed enzymes constitute a program. They determine a set of operational sequences which, interacting under normal conditions with each other and the environment, do

produce in detail the vastly organized nervous system and the whole body. [Indeed, when the two halves of a cat cerebrum are functionally separated by operation, Sperry (268) found them to be more nearly alike in learning ability than are the brains of two different cats, much as identical twins have like intelligence quotients.] Similarly, the equation for calculating *pi* can produce as many hundreds or thousands of detailed digits as one cares to grind out of it. There may well be many interdependent sets of rules in the nervous system for handling information which we have not yet learned, so that the number of details stored as such, and the attendant storage capacity, may be far less than is currently assumed.

Besides the inborn information, all developing nervous systems undergo further molding and fixation which, under the constant environment of early embryonic stages, is practically universal to the species. Pieces of the young neuraxis can be rotated or turned end for end or displaced longitudinally, and yet reach normal form in the new locus and establish appropriate connections (55). Small nerve roots can be led to large peripheries or large ones into small peripheries, during embryonic development, and will re-establish an appropriate quantitative adjustment of size of nerves and number of fibers (291). Peripheral connections, both sensory and motor, can be tangled operatively, yet the central functional patterns re-form to give normal integrated behavior (268). Some microspecification of the neurons and junctions is thus indicated, much as for the later processes of individual learning and the accompanying formation of memory traces.

In both cases, also, actual growth of some sort is further indicated, a function that may fall off with time, rapidly at first and then slowly, perhaps along a decaying exponential curve. In any event, modifiability of the nervous system is extreme in the very early stages when major operative insults can be corrected, decreases rapidly until birth when major patterns are irreversibly established and even anatomical regeneration is circumscribed, and then more slowly throughout youth and old age when learning and retaining new patterns becomes ever more difficult and ultimately practically impossible.

INDIVIDUAL EXPERIENCE. Yet much important pattern formation still occurs in infancy and youth, and is, of course, ever more determined by individual rather than by universal experience. Something like imprinting may well occur in man as well as in ducks; certainly such attitudes as fear of snakes and shame at nakedness are inculcated early and indelibly. [J. G. Miller (personal communication) observed a woman in deep coma, lacking optokinetic reflexes and with bilateral Babinski reflexes, who pulled down her skirt when exposed for examination.] Avoidance conditioned reflexes may extinguish only after autonomic nerve section (297). Conditioned visceral reflexes to pain or fear or disgust, in dog and man alike, can be established early and endure through life (76, 178). The Australian aborigine, condemned by the tribe for some transgression to have the 'bone pointed' at him, retires and dies on such a basis. The infant chimpanzee or human, raised for the first few weeks or months of life in the absence of pattern vision, can never develop this properly. Although the eye may later be available as a normal optical instrument, the nervous system has apparently 'set' too far for the missing architectural patterns to be established then by the same functional activity that would earlier have succeeded in doing so (245). An especially dramatic example of the importance of experience in laying down material patterns, and one showing as well the importance of pre-existing patterns on which new ones can build — again much as the molecular template for macromolecule reproduction is afforded by the removal of one occipital lobe of a rat, followed in 2 weeks by the removal of the other (207). Before either operation, pattern vision is normal; after the second, it remains present if the animal were allowed normal visual experience during the interval between operations; it is absent if this experience was prevented.

On the positive side, motor skills are more nearly perfect when learned in early life; the athlete or the musician who rises to the top has begun training almost in infancy. Only one's native language, or others learned early, is spoken without an accent; foreign adults cannot usually master the English 'th' or the French 'r.' Trigger points, set up experimentally or by accidental trauma, may endure for life [see Gerard (101)], as a fingering error made early in learning a composition may dog a musician's performance ever after. Similarly, if some cerebellar efferent connections to spinal neurons are severed even a few hours before others, an enduring postural asymmetry may be established in the spinal cord (Brookhart) — as, indeed, the order of removal of the right and left cerebral cortex determines the direction of circling. Even the mental and perceptual abilities and the more general intelligence quotient undoubtedly contain, besides inborn capacity levels, considerable components depending on individual

experience and exercise. Indeed, even so slight and transient an experience as the perceptual distortions produced by saturation in figural afterimages of vision, touch and proprioception (160) can last for months after a single experience (292).

*The world image.* The raw experience of the infant is progressively categorized and differentiated to the highly discriminative perceptions and conceptions of the adult by successive steps of patterning in the nervous system. The larger categories are established early, the lesser ones fall within the limits set by these, finer and still finer ones forming in turn, each smaller discrimination coming later and being less fixed than the larger category. So leaf petioles and twigs and branches and boughs develop from the initial stem; so a geometrical doodler forms a large triangle and then divides this into smaller ones, and these into smaller ones, down to the limits set by pencil lines. Constant or regularly repeated constellations of sensory inputs generate the entities of our universe of experience, initially the material objects. This experience is not at first referred to the outside; to the infant all is 'I.' Later a 'not I' or 'thou' is separated and only still later is the personified 'thou' further divided to discriminate the impersonal 'it.' Then come the major categories of material entities, then the functional ones, and so on.

At each stage greater abstraction, as well as particularization, is attained. This corresponds to the inevitable filtering and loss of incoming information, but the category, like a coding rule, allows more to be retained and used. The way in which a terrain is conceptually mapped in three dimensions by primitive mountain people under the guidance of sophisticated Europeans, and the comparable way in which a child grasps spatial and logical relationships has been beautifully described by Bronowski (33). Schilder (261) and Piaget (231) present like material. Only after extensive overlearning of a finger manipulation does a subject develop a visual image of what has been learned through touch and proprioception (190; see also 35). Similarly, the well-experienced pilot, handling his controls in an emergency, often 'sees' the entire plane, as if watching it in free space, respond with appropriate maneuvers.

Learning, on perceptual, motor and ideational sides alike, probably involves the formation of pattern elements in the brain, partial assemblies or the like [cf. Milner (212)], which can then be combined into larger and still larger functional wholes. The telegrapher, learning to receive Morse code, improves to plateaus of letter recognition, word recognition and, finally, phrase recognition; new gestalts are formed or, in modern terms, bits of information are grouped into chunks (208). Motor skills are similarly built of established acts, each usable in many complete repertoires (Paillard)—as in mastering different piano pieces. And, of course, the new arises in imagination by a similar recombination (94, 112).

When elements used in some performance have been learned and previously used in like relations, they fit easily and are compatible (73). Performance on a problem is then faster and more correct than when incompatible sensory and motor components must be brought together. When new combinations are required, conversely, learning is far easier because of the pre-established elements than if the brain had to start at scratch—witness the inverted manipulations under a microscope or the use of esophageal speech after loss of the larynx (Zangwill). In the reverse direction, with loss of functional capacity, as in aging, integrated behavior fragments back to its components. Even lack of practice causes such forgetting regression, and this might be related to the phenomena of sensory deprivation. At least, visual rhythms are abolished after hours of darkness (60), just as they are broken by patterned light.

Timing is obviously critical in such combinative processes. This may account for the disruption of thought and speech by delayed auditory feedback. The presence of properly timed potentials, appearing in both specific and nonspecific systems, only when the correct behavior follows a visual flicker stimulus, is a case in point (152; see also Galambos & Morgan). The marked differences in perceived patterns when a stroboscopic field is displayed to one or to both eyes (266, 267) is a related spatial phenomenon. Similarly, in normal development, when strabismus gives double images, impulses from one eye become suppressed and, on the motor side, one hemisphere comes to dominate the other—there is no language defect in children following damage to the speech area of either cortex (Zangwill).

The traces left by experience are real and specific patterns in the nervous system, with morphological locus and physiological properties. True, at first there is widespread participation of brain neurons (Livingston; 21, 147, 183), especially with meaningful stimuli (77), and much freedom as to which groups finally become 'channelized' for particular functions; nevertheless experimentation, such as the evocation of specific memories by punctate stimulation of the temporal lobe (Penfield), is rapidly bringing these traces from the realm of postulated constructs to that

of real and manipulable entities. Other visual experiments extend the occipital lobe results already mentioned.

Thus, when the optic chiasm has been cut in cats so that only the ipsilateral projection area is activated from each eye, a discrimination learned through, say, the left eye is correctly performed when stimuli reach only the right one. After further section of the corpus callosum, however, the discrimination is retained only for stimuli presented to the left eye, not for those to the right eye. Clearly, the learned pattern has remained localized to the left side of the nervous system, although it could effectively be engaged by the right side so long as major connecting paths were intact (59). (The above findings were for pattern vision; results for color vision did not indicate such sharp lateralization.) Learning 'set' also fails to transfer from the side that learned, even when specific discrimination does, with intact callosum (268). In this connection, the finding of Land (166) that all spectral colors can be experienced by a normal subject on looking at two superposed images of a scene, each taken at a different fairly pure spectral frequency, is relevant. (Also, rotating black-white disks can give colors, as described by Bartley.) The qualitative experiences are generated from quantitative differences in intensity, and the various shades plot as geometrical displacements from a black-white axis.

On the motor side, also, not only is much of the cortex involved in language use, but temporal lobe stimulation can interfere with word choice or can even block speech (Zangwill), just as frontal lobe stimulation can lead to maintained reiteration of a word (30). (Such findings would seem to demand cortical action rather than the subcortical control urged by some, including Paillard.) It would be naive to think too simply in terms of gross regional memory chunks (102); witness the aphasic loss of only one language in a bilingual person [e.g. Lambert & Fillenbaum (165)]. Such subjective findings, related to the objective evidence from electrophysiological localization in projection and association areas, afford ways of actually plotting anatomically the patterns of experience and conception. They are fragments of the total representation of external reality in a microreality internal to the brain, as developed by Craik (49), and go a considerable distance to remove the mystery of qualitative subjective experience and to link solidly our subjective world to a real external one in a pretty good one-to-one relationship — a resolution of the problems that engaged Berkeley and Hume.

*Mechanism*

The nature of the material trace, and the conditions for its establishment, are also being explored. Not only can memories be localized, they can be favored or hindered by the activity of specific neural regions [the reticular formation and amygdala, considered by French and Gloor; the hypothalamus by Doty (57) and Gellhorn (80)] and, once laid down, can be brought into clear or blurred recall by stimulation of other particular brain regions (26, 149, 222, 259, 275; Galambos & Morgan). Hippocampus stimulation blocks learning at first, large slow waves appear in it with habituation but desynchronize with the novel (126). Large slow spindles in response to a conditioning stimulus predict failure to learn (21). Early in training, hippocampal potentials appear before entorhinal ones; later the time order is reversed (3). Loss of recent memory after damage to the amygdala, mamillary bodies (257) or fornix (274) has been noted. These regions presumably act via modulating impulses that favor or hinder the initial flow and reverberation of impulses laying down traces, or the subsequent flow involved in recall.

The problem of specific recall, like that of directed attention or of selected action, is not yet clearly related to particular brain mechanisms. Some sort of exploring or scanning-type process, that runs through categories as a card-sorting machine, may be involved. The vast detail that is retrievable, especially under hypnosis, is well known, but the process of its retrieval remains mysterious. Serious workers report, for example, that a hypnotized adult can recall details of a classroom attended when 6 years old, but only after being first given the suggestion, "You are now six" (262). Also, details of a conversation held by a surgeon and assistants during the period of full surgical anesthesia have been subsequently reported by the patient under hypnosis (41). Recall is perhaps more important relative to storage than has been generally believed.

That activity of a neuron and junction leaves behind an altered state has been known since the recognition of a refractory period of nerve. Even earlier, it was well established that after-potentials were markedly prolonged and enhanced by a tetanization as compared to a single action (289). Tetanizing presynaptic fibers can enhance for a long time reflex responses evoked through them; conversely, weeks of inactivity can practically abolish a response (62, 186). Following a single nerve fiber action, after-potentials may last seconds, chemical activity, minutes, and ion pumping, hours. After a

few seconds of tetanus, the potential changes can last for minutes, the metabolic and threshold alterations, for hours, and synaptic transmissivity changes, for days. There is now much evidence that many minutes must elapse between having a sensory experience and establishing a permanent memory of it (61, 102, 171, 227, 237, 278, 279; Galambos & Morgan). This period for fixation may well involve continued reverberation of impulses in the appropriate neuron nets; and with some hundred thousand repetitions possible in the fixation time, a relatively enduring trace is left, rather than a quickly reversible alteration.

A dynamic memory thus precedes a structural one; and interruption of the dynamic process, by cold or electroshock or anoxia, as well as its modification by temperature (238) and drugs (236), give results which fit well into such a neurophysiological interpretation. The memory blank after an ictal seizure is likewise explicable by mass discharge that precludes reverberation (see also Gloor). If the amygdala indeed controls fixation (Gloor; 224), this might well be by altering cortical neuron potentials, and so thresholds and the ease and duration of reverberation. Strychnine has been found to shorten fixation time (Krech, personal communication), presumably by such an action. Indeed, the lasting memory of emotionally charged experiences may depend on such enhanced reverberation resulting from action of the nonspecific system to lower thresholds. A more detailed model in terms of neuron sheets, and some behavioral inferences from these considerations, will be presented later. It deserves note now, however, that functional rather than spatial parameters may be important in storing information (Neff). Different receptor elements activate different kinds of fibers and reach central neurons that differ in properties as well as position. Such physiological variables as kind of substance released, shape of potential generated, time constants, and the like may be of great importance.

## BRAIN AND BEHAVIOR—SUGGESTIONS

Guesses guide experimentation; nowhere are they needed more than in relating the brain to behavior. This section deals largely with such guesses. If they stimulate only their experimental demolition, or in other ways lead to better ones, they are justified.

### *The Physiological Neuron Reserve*

Turn now from patterns of architecture that endure in time back to those of activity which are evanescent. Much has already been presented on these, but further attention must be directed to the number of neurons active and to summation, irradiation, reverberation and their consequences. The value of a large population of neurons to a complex and variegated behavior has been briefly considered.

With fewer neurons available, fewer categories can be established, fewer patterns laid down and the like. Cortical ablations do not affect simple sensory thresholds or motor acts; these are cared for by more ancient structures. [Even here, triploid salamanders, with larger neurons than normal but only two thirds as many, show an impoverished behavior, according to Fankhauser *et al.* (68).] But more complex and discriminative behavior is lost as cortex is removed—patterned vision or patterned hearing (the tone sequences, ABA versus BAB) goes with the projection areas (Bartley, Galambos & Morgan; 216) and conceptual analysis or the level of difficulty of a problem that can be solved collapses with the restriction of cortical mass, just as the skill of movement decreases with less motor cortex available (Denny-Brown). Only with the great richness of neurons in his cortex can man stand away from the immediate input sufficiently to achieve important generalizations, apply normative criteria, guide responses by distant goals, use abstractions and 'bind time.' The relatively slight behavioral defects so far found with hemispherectomy may represent a real bilateral duplication of function or, perhaps more likely, may result from inadequate tests. Improvement in brain-damaged children by such an operation can be attributed to elimination of conflicting abnormal neuron activities. Whether the essential unconditionability of spinal cord is due to inadequate neuron supply or to qualitative neuron differences is an open question. Actually, enduring reflex alteration following transiently altered input does occur in the lower cord (101; Brookhart).

Anatomy, however, merely sets an upper limit; the physiologically available neurons rather than the anatomically existent ones must determine behavioral capacity at any time. This physiological neuron reserve could be reduced from the anatomical population in two ways; some neurons may not be accessible to activation at that time, others may already be activated and fully engaged in routine performance. The physiological reserve must increase as neurons have their thresholds lowered, as by epinephrine or alerting impulses from the reticular system, or by increased neural bombardment resulting from continuing input with progressive summation and irradiation, and ultimately reverberation, of

impulses (54, 105). The reserve must decrease when reverberation continues until serious channelization develops, as in maintained tension and anxiety and, probably, in the neuroses (108, 109, 114). Gastaut & Fischer-Williams note a similar double basis for convulsive activity—lowered threshold, as with pentylenetetrazol, or excess stimulation, as in photic driving—and the absence of consciousness with either too little or too much cortical activity (see also Bartley, Gloor). Increased thresholds, produced by hypnotic drugs directly or by inactivating the diffuse system, would also drastically decrease the reserve; and it is tempting to guess that the unconsciousness of deep sleep or anesthesia is simply the consequence of too few active neurons.

It is probable that the phenomena described by psychiatrists with the unfortunate term 'psychic energy' [see Colby (46)] can more reasonably be accounted for in terms of the size of the physiological neuron reserve. When this is diminished, temporarily or permanently, there is an accompanying constriction or stenosis of behavior with greater stereotypy and repetitiveness, decreased exploration and invention, and a lowered intensity of consciousness. A moderate degree of stress and unresolved problems posited by the environment would bring more and more neurons into action, first by summation and irradiation and later by chemical reinforcement through release of epinephrine or a comparable substance, and through facilitating or alerting impulses from vigilance centers. This evokes, first, awareness; then, more patterned consciousness; then, focused attention or alertness or vigilance, associated with increasing tension and anxiety.

Beyond an optimal level of emergency marshalling of the resources of the brain, as well as those of the body, more intense continued input overload leads to a breakdown of functioning (211). [Tachistoscopic performance is enhanced by mild stimulation of the reticular formation, disrupted by strong stimulation (Bartley).] Reverberation presumably now occupies a larger fraction of the neurons, rendering them inaccessible to the play of shifting activity patterns; vigilance progresses to mania, tension becomes unstructured anxiety, performance shifts from flexible exploration to unadaptive and rigid repetition, and psychic energy is dissipated (116). Marrazzi (194) suggests a reverse mechanism for such psychotic phenomena as hallucinations. This assumes decreased cortical control of lower centers and their consequent release, the whole related to an inhibitory action of epinephrine. Fatigue, hypoxia, drugs and various other means of disturbing the normal metabolic activity of neurons can similarly bring about temporary or enduring stenosis of behavior. A promising simple test of flexibility and creativeness is to have a subject tap two keys in random fashion (Kornblum, S., unpublished observations). With fatigue, randomness degenerates into repetitive patterns, with runs of simple alternation—suggesting the lapse into autistic behavior. Similarly, one would expect that, with moderate tension, decision time per bit (normally .125 sec.) would decrease, but that with severe tension the time would prolong or the response would become stereotyped and errors increase. These views have been extended elsewhere (113, 114) to the manifestations of schizophrenia and of old age—the limited capacity decreases the possible conceptual classification and so leads to the regression of schizophrenia to predicate reasoning, personification, loss of self boundary and the like [compare Arieti (11)]; as well as to narrowed attention [see Callaway & Dembro (40)]. The greater loss of word usage in aphasias with greater random loss of neurons (Howes, D. H., III, Geschwind, N., personal communication) is quite comparable.

*Physiological Parameters*

The relation between brain structure and behavior has been studied for centuries and much is known concerning the contribution of various brain regions and nuclei to all aspects of functioning. Comparable efforts to relate performance differences to physiological properties of the nervous system are almost nonexistent. Yet it seems highly probable that the finer nuances of perception and performance, of personality and ability, will depend more on physiological parameters than on anatomical ones. The physiological neuron reserve, in contrast to the anatomical neuron population, accounts for many properties of consciousness and behavior. It can hardly be questioned that physiological differences in single neurons or synapses or interaction patterns—quite aside from the momentary discharge or no discharge of impulses—will importantly influence the individuality or personality of the organism.

Key variables for the neuron would be: its metabolic rate and quality and consequent drug sensitivity (such differences in neurons and synaptic mechanisms must underly the specificity and the variance of drug action); the existence and properties of a spontaneous electrical rhythm; the normal threshold level and the spontaneous play in threshold;

the ease of summation of incoming stimuli and the kinds of stimulus patterns to which the neuron is exposed; the degree of accommodation; the duration and character of refractory periods; the magnitude of posttetanic changes; and the like. Similarly, for interaction patterns of neurons such variables come to mind as: the strength and form of steady potential fields; the strength of synchronizing mechanisms and the ease of desynchronizing neurons; the power of feed-back controls at junctions; the ease of setting up reverberating chains and loops; the ease of altering the number and arrangement of neurons in such an assembly or in a still larger table of organization; the ease of irradiation through neural nets and masses; the speed and firmness of fixation and the amount of reverberation needed to produce it; and the like. And at both levels there could be important differences in the statistical range and pattern from one individual to another, as in timing and duration of discharge from cell to cell.

Some intriguing guesses can be made relating personality attributes to physiological properties. (Walter's EEG parameters—abundance, versatility, etc.—and their relation to individual performance constitute an approach of this sort.) Defective fixation, for example, seems to underly presbyphrenia, the failure of aging brains to hold recent memories. Too easy fixation would lead to great and detailed memory storage, but with little flexibility in handling this information beyond recalling it—the usual quiz kid type. Defective synchronization would make for distractibility, and excessive locking of neurons would give a narrowed attention and a 'tubular personality.' [It is interesting in this connection that airplane pilots tend to give 'tuning fork' EEG records, as reported by Williams (295) and Kennard (personal communication).] Excessively stable thresholds, similarly, would lead to rigid personalities, the petty official type; excessive threshold fluctuation would be associated with a flight of ideas. High fluctuation, but not quite so high, should favor imagination and creativity. As mentioned, the specific neuroactive and psychoactive agents presumably act upon such physiological parameters even more than upon anatomical loci. All, in turn, depend upon molecular and metabolic properties—as the convulsion proneness of mice with low brain ATP (1) or the poor learning of rats with low cholinesterase (162, 254; see, however, 42). When these have been explored, a comparison with the behavioral effects of these agents will show the extent to which such guesses as the above are sound [see Korey & Nurnberger (161)].

*Reverberation*

Convergence and divergence of nerve paths and impulses is the rule. In autonomic chains, one presynaptic fiber can activate nearly 40 postsynaptic ones (Hillarp). In the central system, precise figures are difficult to come by, yet there is clear evidence of both arrangements (Lloyd)—just as many enzymes may make a gene and many genes, an enzyme. If inhibitory feed-back loops did not prevent, incoming messages would probably 'explode' up the neuraxis (Bartley), as in trigger-point pains; and normally there is a considerable amount of avalanching, for impulses from single receptors are picked up along the afferent path with gross electrodes (121) and are widely picked up, as on the motor side, with microelectrodes (Patton & Amassian). Yet the summation resulting from convergence is also essential—witness the increasing number of optic nerve fibers that must be excited to enable activity to reach further and further into the nervous system (Bartley). The sequence that results from convergence—spatial and temporal—is summation, irradiation, reverberation and fixation.

The balance of positive and negative control has been touched on in several connections, since both phenomena may be involved in most neural processes. Activation of additional neurons can involve removal of inhibition as well as addition of excitation. The following treatment is mainly in terms of summation, which probably dominates in immediate stress situations. Inhibition (or the subsidence of general irradiation and so of facilitating interneuron bombardment) is perhaps most important in long-range learning phenomena.

INNOVATIVE BEHAVIOR. Experience establishes appropriate stimulus-response relations and the necessary open channels in the nervous system to mediate these. During the learning process, activity irradiates widely, even to the autonomic system (Halsted); many irrelevant motor actions accompany the relevant one (as the child grimacing and moving its tongue while its hand laboriously makes early letters), tension and attention are high (Paillard) and many neurons in the cortex and deeper structures are active (2, 20, 147). With learning and the establishment of specific skilled responses, the irrelevant movements drop out, muscle tension falls (Halsted), and many

cortical and deep neurons, previously engaged, now remain silent. Similarly, habituation is associated with a general decrease in response to the familiar stimulus (149). Errors are associated with reappearance of electrical activity and, when different flicker frequencies signify plus or minus reinforcement, with different response rates in the cortex and subcortex (152). Learning, thus, involves the inhibition of neurons that were earlier engaged while an appropriate response was being established; but diminution of irradiation as effective channels are formed (see below) may also be involved. In much the same way, a computer that can 'learn' will first explore all possible actions, as the next move in a chess game, but later will not bother with those that have regularly proved worthless.

Whether inborn or learned, automatic reflex behavior cares for the routine adjustments of living and is attended by little or no immediate consciousness. One scratches an itch—as one walks—with no attention to the act. When, however, the routine response does not eliminate the disturbing stimulus, messages continue to pour into the nervous system, summate at the early junctions and irradiate to new ones outside the usual pathways (Gastaut & Fischer-Williams; 151). The longer the input continues, the greater the irradiation, until such emergency structures as the diencephalic autonomic centers and the reticular formation are thrown into activity—perhaps via the amygdala (Gloor; 195, 196). The former, through liberation of epinephrine or related substances, directly lowers the thresholds of neurons;[4] and the latter, by increasing the activating bombardment, indirectly does likewise. The result is a still greater irradiation and probably a much increased reverberation. New responses appear and follow one another until a successful behavior finally eliminates the disturbing situation.

This is innovative or creative behavior, replacing the routine reflex behavior, and with it appears increasingly intense consciousness. [Yet much imaginative creation proceeds unconsciously (94)]. In parallel with the idea of a wakefulness of necessity (159; see 136), one might speak of a consciousness of necessity. This is presumably first a simple awareness, involving midbrain and hypothalamic structures (Penfield, Ingram), especially the reticular formation arousal system. Later it increases to attention and then to a high level of vigilance (French), as in the cat watching a mouse hole or the sheep dog quiveringly alert to his master's command and his charges' movements. Affective responses enter as the hypothalamic and limbic systems are aroused (MacLean), with pain or displeasure, and with increasing anxiety, as the functional neuron reserve of the cortex is engaged. Perhaps the role of the periodic inhibitory discharges of sleep is to break the continuing reverberations, and so to prevent excessive fixation and to release reserve neurons. (A comparable suggestion is made by Walter regarding delta waves; indeed, as noted, descending inhibitory impulses are probably essential to prevent explosive avalanche conduction up the cord, as reported by Bartley.) The block of inhibition by strychnine (Grundfest) is similarly explosive. Besides the general level of consciousness and mass arousal effects, the content of consciousness is no less important. This depends on the particular activity patterns, determined in turn by the structured residues of past experience and by the organization of contemporary input. As more of such neuron assemblies enter into activity, reason and imagination appear in consciousness, and insightful problem-solving behavior replaces routine or random actions.

TENSION. There is much evidence that even brief inputs continue to reverberate in closed loops, or set up continued synchronous activity, rather than simply pass unidirectionally through the nervous system. The effects of such stimuli far outlast any possible direct throughput time. Evidence has already been presented that activity continues for minutes and hours, during which a transient experience produces an enduring memory trace. Similarly, unfinished business, the 'unconscious work' of anxiety, dreams, unsatisfied drives and

[4] The inhibitory action of epinephrine has been recognized for some time (192, 193), the excitatory action, only more recently, although a rebound from inhibition was noted by Marrazzi. Besides evidence summarized elsewhere (114), the following points are made in this volume on epinephrine activation. It prolongs pentylenetetrazol convulsions (Gastaut & Fischer-Williams), increases receptor excitability and the size of the Pacinian generator potential (Gray), facilitates the action of acetylcholine on the muscle end plate (Fatt), increases brain oxygen consumption (Sokoloff), and stimulates neurons in the hypothalamus and the upper midbrain reticular formation (Ingram, Jasper). French regards the exciting action on the nervous system in general as secondary to the peripheral action of epinephrine in enhancing proprioceptive input, but this is excluded by the findings of Sigg *et al.* (263). Moreover, the original value of such an inhibitory action, as a negative feed-back mechanism on autonomic ganglia (192), is reduced by the evidence that norepinephrine rather than epinephrine is the orthosympathetic transmitter (von Euler), and even its inhibitory action on such ganglia is disputed (Hillarp).

unresolved tensions [the awaited message, the unsolved problem, the unmade decision, the unassimilated novelty and the unbalanced emotional equation (109)] would be associated with long-maintained reverberation. (If reverberation is in the amygdala in dreams, as suggested by Gloor, a subject with a stimulating electrode in this structure might remember a dream on being awakened just after stimulation; otherwise, not.) The progressive building-up of 'physiological inflammation,' which might be hypersynchronization or excessive reverberation, should also be recalled. Gastaut & Fischer-Williams speak, comparably, of ephaptic spread of activity in the neuropil, 'like oil,' when bombardment is high or threshold low; but they emphasize irradiation via deep centers.

PERCEPTION AND ATTENTION. Reverberation is probably no less involved in much shorter range phenomena. Repression (as studied, for example, by the inability to recognize forbidden words tachistoscopically), subliminal perception (210), autonomic responses to stimuli subliminal for consciousness, the ability of a bright flash as long as 25 msec. after a patterned exposure to block recognition of the latter (Lindsley; 181), and like findings all suggest (105) a reverberation over milliseconds or seconds even in the primitive perception of a stimulus (see also Livingston). Continued neural activity may thus be involved over milliseconds to years in various junctions.

The mechanisms for directing neural activity into one or another set of channels, and so focusing attention on one or another input (from outside the body, from within it or even from within the nervous system), or selecting an output, are but little understood. The feed-back loops altering sensitivity of the receptors and the input channels, and the role of higher structures in modulating these with habituation or vigilance, are receiving intense study (French, Livingston; see also Fry on accommodation, and Paillard and Eldred on the efferent side). A similar diencephalic influence on the cortex, partly expressed through the alpha rhythm, has also received much attention. But none of these really accounts for the selectivity of action, and the figure of the diencephalon directing activity as a cathode ray gun (96) also leaves the mechanism of control vague. Miller and co-workers (209) are developing a model that deals with 'plans'—programs—for action appropriate to the external environment. [Compare the 'scheme of action' of Bianco (Paillard).] Their origin is unassigned; but one is selected, or substituted for another, by the frontal cortex, and the limbic system handles its execution. One might regard the hypothalamus as similarly selecting and in part executing plans for handling the internal environment.

*Feedback*

RECIPROCAL INHIBITION IN CONSCIOUSNESS. The demands on attention cannot all be met; input at all levels exceeds output by many fold, and the mechanisms worked out by Sherrington for control of the final motor path must largely apply to the capture of attention. Certainly attention, like behavior (and recall), is normally shifted abruptly in an all-or-none fashion towards one or another of competing outcomes rather than split between them. There is a clear reciprocal inhibition of the Sherringtonian type between perceptions (Neff), feed-back controls (Ström), different emotions (as sexual arousal and anger), emotions and ideas, and various directions of attention. The driver hears nothing of an interesting conversation during a traffic emergency, as the student finds a chunk of a lecture displaced by internal ruminations. The mechanism, inhibition of neighboring units by recurrents from the axon, that operates in a retina to emphasize an edge and in a motor pool to give clean movements, Renshaw cells, may well be widely present to gate all central flow and sharpen the selection of alternate channels. The widespread presence of Renshaw-type cells is now an active question. [See also Milner (212).] The careful studies of Broadbent (32), mainly on auditory competition for attention and response, clearly indicate brief lapses or blinks even in attention continuously directed to the same input. His model, in terms of channel capacity and other communication mechanisms, will be considered later.

AFFECT AND DRIVES. Arousal, attention and vigilance are also closely related to the internally initiated drives concerned with the maintenance of homeostasis. Actually, such drives, which imply an external behavioral component, also really originate outside of the organism; they are part of homeostatic mechanisms involving negative feed-back loops extending into the environment. (Less directly, sex behavior and curiosity may also involve these.) External cold, acting through thermoreceptors on the body surface or in the hypothalamus, can bring about integrated internal responses for increasing heat production and decreasing heat loss. In addition, the central thermoreceptors activate the EEG, increase muscle tone

and in general enhance vigilance. Conversely, a high temperature leads to somnolence and inactivity. Chemoregulation likewise involves peripheral and central receptors, and a general behavior pattern and activity level appropriate to lack or surfeit of external food supply. The important role of the hypothalamic-pituitary system in these and other regulations has been fully described (Stellar, Harris, Ingram, Sawyer), and the special sensitivity of hypothalamic and related neurons to chemical influences has been noted.

GOALS. Closely related to drives and their associated emotional tone are the problems of goals and feedback and the value hierarchy. As a given physiological constant (or related equilibrium) is further and further displaced from its equilibrium level, more and more powerful homeostatic adjustments are activated, and internal and external behaviors become directed to the prepotent goal of restoring this displacement. A stress is such a displacement; it leads to irreversible damage only when the limits of homeostatic tolerance are passed. The closer the approach to the tolerance limit, the more vigorous are attempts to correct the displacement and the greater is the prepotency, or 'value,' of doing so. Acclimatization can reset the physiological zero and so alter the goal to which these adjustments strive; the environment operates, via natural selection, on such stress adjustments.

In the psychological realm, the situation is similar. The physiological zero for activity, alertness, vigilance and behavior in general is not at the absolute zero level of somnolence, sleep, inactivity and inattention. It is somewhere between this equilibrium level and the other pole of continued change, adjustment, tension and vigilance. In the adult, too little environmental challenge leads to boredom, restlessness, even hallucinations; too intense a challenge leads to fatigue, anxiety and finally sleep. Presumably the adult mammal, at least, tends to regulate the physiological neuron reserve at an optimal level of partial activation of neurons, which makes them easily accessible, and with little over-reverberation or over-synchronization, which tends to withdraw them from the pool. It is impressive that mankind, with access to a variety of stimulant and depressant drugs, has tended to adopt both on a wide scale, but with the stimulants dominating (107, 144).

Attention is directed to a considerable extent in terms of goals or 'purposes'; so values—perhaps just 'significance'—must be 'givens' at any time (cf. MacLean). They have been established by experience, racial or individual, and are related to survival. Outcomes of action, rated 'good' or 'bad' on such criteria, can reinforce or attenuate future acts—by reasonably understood mechanisms, discussed later—and so establish a hierarchy of choices embedded in the nervous system. Much of this learning presumably involves the diffuse sweep of evolution; more altruistic goals have increased relative to more selfish ones (66, 90, 99). Care of the young, sacrifice for fellows, adherence to loyalties all mount with the development of the neocortex (92); and monkeys raised in a social group are cooperative, with many social attributes, while those raised alone are hostile (132).

### *Subjective and Objective*

Other behavioral consequences of neurophysiological mechanisms have to do with the formation of an interior brain model of the external world, with categories and universals and particulars, with memory and recall and forgetting, and with insight and imagination and conceptualization. All these have been touched upon earlier, along with the problems of decision, of perception and attention, of motor patterns and sequences and the development of skills, and of concept formation.

One last note is due on subjective experience and objective behavior. The latter depends on efferent nerve impulses to appropriate effectors. These neurons are fired by impinging impulses from other neurons, and so by regresson to the afferent messages from receptors. But it is clear that not all entering messages or information bits find their way out in prompt action; some, probably most, end by altering the material nervous system and become stored memories or information. With reverberation and feedback and synchrony, much can happen within the brain—and presumably accompanied by some kind and intensity of consciousness, including the unconscious—with no immediately correlated behavior. Conversely, from this rich central store overt behavior can flow which is not immediately related to any input. Such separation in time and type (and locus) of stimulus and response gives the richness and spontaneity of behavior experienced as volition and rationalized as free will. Behaviorism is thus too narrow a straight jacket comfortably to contain the mind; but the alternative is not the 'uncaused cause' of a choice by the psyche. Whatever the degree of contingency at each level or organization, there is no place for a directed random event, and a general

chain exists—of causality down levels and of purpose up them (93, 97, 110).

MODELS

A fitting culmination of a chapter such as this is an examination of the conceptual models that have been developed to understand the workings of the nervous system and to predict its performance under various circumstances. A great variety of these has been offered, varying from direct inferences regarding neuronal activity, based on neurophysiological experiments, to formalistic considerations of hypothetical entities in certain mathematical relations. Most efforts have been primarily at the neuronal level [e.g. Craik (49), Milner (212), Smithies (266)] or primarily at the formal [e.g. Culbertson (51)] or the philosophical level [e.g. Smithies (263)]; but the most useful ones have attempted to develop the mathematical relationships from the known properties of neurons, using experimental values for the parameters of the equations [e.g. Rapoport (240), Barlow (15)]. Most recently, models built upon communication engineering and information flow have joined the parade [e.g. George (81)].

Certainly, with advanced neurophysiological knowledge, and with the development and application of appropriate mathematical tools, especially those of relations rather than of quantity (and with improved communication between those in the separate fields and with effective interdisciplinary training), models have increased in power and sophistication. Some begin to have the sort of precision and elegance that generate both confidence in their congruence with reality and the emotional satisfaction associated with achieving a real solution. The physiological discoveries have all been in the direction of giving greater freedom to the functioning nervous system—freedom in time, in quantity, in locus and in variability of performance—so that now the pattern of activity is critically in focus, and pattern is information or organization, the trade mark of living organisms. Since adequately tracing the development of models is out of the question, important advances will first be summarized and then two of the more recent and satisfying models will be given as examples.

It need hardly be urged—except that some might regard model building as 'mere speculation' (e.g. Gernandt)—that theories or models enable man to expand the possible world in his grasp, just as experiments enable him to restrict the possible toward or, hopefully, to the actual. The problems today are to explore the consequences of various assumptions as to the dynamics of groups of neurons, as multiple properties range over permissible ranges. The use of computers to simulate 'brains' with assigned attributes is beginning to pay off, as noted earlier; it is a relatively cheap pretesting procedure to sharpen the experiments with real brains.

*Bench Marks of Neurophysiology*

To present an evaluative summary of basic factual and theoretic advances of the past century is rash; but here is one nonetheless.

AXON PROPERTIES. That nerves carried messages was known to antiquity, but it was believed that they served as passive conduits for hypothetical fluids or vibrations. Over a century ago, the discovery of resting and action potentials and the measurement of conduction velocity indicated the active participation of the nerve in conduction; and this was fully borne out by the demonstration, in the first half of this century, of the refractory period, the thermal and chemical changes associated with activity, and the impedance changes. Establishment of the all-or-none, or digital, behavior of the active nerve fiber fully supported the core-conductor model of a propagated activation. Depolarization of a region activated it and dropped its resistance, thus generating eddy currents which depolarized and so activated a succeeding region. This model accounted elegantly for a vast number of factual details, including such influences as fiber diameter, myelin and internode length on conduction velocity. It did not account for the explosive membrane change and the events leading up to it, nor did it pay any attention to the delayed events following a single nerve action.

More careful examination of the membrane potential and related properties revealed local potentials that might oscillate or increment after a brief shock, showed spontaneous threshold fluctuations and, particularly, encountered the positive overshoot of the action spike. The depolarization and eddy currents were, therefore, also active responses of a living nerve rather than passive physical events; indeed, for short neuron processes, electrotonic currents may be the sole agent in activation spread. The model that now emerged supplemented the older one and related membrane resting potential to the internal-external potassium ion ratio, the action

spike to that of sodium, and the whole activity-recovery cycle to differential permeability changes. Such a picture obviously demanded energy for pumping ions and recharging the system, and various relations have been seen between the delayed heat and chemistry and the after-potentials; but no inclusive model relating metabolic events to physiological properties has been developed. (G. Ling, in an extensive monograph on his fixed charge induction hypothesis, soon ready for publication, does supply a general model of this type.)

With the need of enduring restitution processes after a brief action, the many cumulative changes with repeated activity became understandable; but a solid quantitative formulation is still lacking for the progressive changes in after-potentials, in spike height, in thresholds, in heat production and oxygen consumption, and in other manifestations of equilibration. Over still longer times it has been established that there is vigorous synthesis in the cell body and steady movement of substances from it down the nerve fiber. The modulation of these processes—for repair after cell damage, to meet the needs of activity, and in relation to experience fixation and information storage—are mostly for the future.

NEURON PROPERTIES. For the entire neuron, as for its fiber, the emerging facts and theories of neurophysiology have given progressive emancipation from the passive and inflexible telephone-exchange model of central activity seen in the simple reflex. Neurons proved spontaneously active, with rhythmic changes in thresholds and potentials; they maintained somatic potentials along the dendritic-axonic axis; and steady potential fields, acting upon these, altered thresholds, rhythms and, particularly, favored or disrupted synchronous activity. These potentials, and their rhythmic discharge, also depended on the cell metabolism, rapidly being unfolded, and on a trip mechanism, probably ionic, operated by the energy flow. Qualitative differences in metabolism between cell groups, even between cell parts, and quantitative gradients along the neuraxis, as well as a mediolateral organization, further led to differing physiological and pharmacological behaviors of various brain regions.

Besides these internal and external steady influences, threshold was modulated by incoming nerve impulses, especially affecting the dendritic pole of the cell. Eddy currents from various cell regions converged upon the proximal axon segment and hillock where their total effect was integrated to produce discharges of varying number and timing, including none. The picture thus became clear of a differentiation of cell regions, part for the storage of information, part for its transmission; and the concept of the synaptic mechanism as a decision point, able to integrate in a continuous or analogue manner the varied stimuli—excitatory and inhibitory, patterned in time and space, present and past—and so to control the presence and pattern of efferent discharges, gained precision.

The junctional mechanism has also achieved complexity and the attendant relaxing of input-output linkage, a result of attention to the types, numbers or strength, and positions of synaptic endings; the character of the receptor sites in the postsynaptic membrane associated with these; the probable existence of transmitter packets; and the analysis of conditions of formation, release, spread and action of such agents, as well as of the longer-known eddy currents.

NEURON GROUPS. Further knowledge and insights have developed as to the interrelations of these neural units, as well as for the units themselves. The model of a closed loop of neurons, supplementing a linear sequence, proved most fruitful, as did the simpler one of an avalanching net of interneurons. These accounted for summation, irradiation and reverberation, and foreshadowed the presence of homeostatic negative feed-back controls. Such networks raise questions regarding the importance of topology versus topography in the nervous system and of the table of organization, describing the balance between central and peripheral and between series and parallel flow of information and decisions. Reverberation (with inhibition), and synchronization, leads to models for the fixation of experience—the laying down of real patterns in real brain loci that are congruent with a real outer world—and also lead to hypotheses concerning personality traits.

When the vast numbers of neurons in man's brain are considered, the dichotomy between specific neural nets and generalized field effects tends to resolve into probabilistic relations. Certainly, specific and diffuse synaptic systems exist and presumably are of prime importance, respectively, for conation and affect, for pattern and level of awareness, for set and program, and for the storage and handling of experience. Between and within these various systems exist the integrative mechanisms, including reciprocal inhibition, as they do for simple spinal reflexes. But beyond these fractionating factors, there remain

properties of an over-all statistical population of neurons, especially when arranged in sheets as in the cortex; and the properties of waves of activity traveling in such a population are leading to exciting behavioral models. Further, the influence of sheer numbers of neurons is beginning to be apparent, and the ideas of a functional neuron reserve and of an optimal activity level help interpret many phenomena in human behavior, especially such reversible or enduring changes as are associated with stress, age, personality and mental illness.

Additional models are appearing rapidly which help account for information handling in terms of channel capacity, availability and redundancy, and of storage, noise and similar communication concepts. Attention is being given to programming mechanisms in the nervous system, and study here will surely yield great insights; but this is still in its infancy.

Finally, as the individual neuron controls its metabolism and so its function, so the whole nervous system is exquisitely protected by homeostatic mechanisms so that its milieu, like that of a fine chronometer, is kept highly constant. Regulation of the cerebral circulation, a blood-brain barrier, active transport mechanisms, special chemoreceptors in the nervous system, special chemoeffectors tying the nervous system to the pituitary and endocrine mechanisms—these and many other highly-evolved devices attest the importance of the central nervous system to higher organisms.

### *An Information Model*

A recent volume by Broadbent (32) summarizes extensive studies on perception, attention and performance, and derives from these data a formal model of the nervous system as an information-handling machine. To some extent the entire nervous system acts as a single communication channel and, therefore, exhibits a limited capacity for which sensory events must compete. (This capacity is clearly related to the functional neuron reserve, considered above, and so to the size of the cortex.) The channel is not captured at random by a few of the vast number of sensory events clamoring for it; certain classes of events—for example, sounds of like pitch or spatial localization—tend to be selected together for transmission. Further, certain types of classes are more likely to be selected than others; which ones gain preference is related to the properties of the stimuli and to the state of the organism. Among the former, increase in intensity or in time since last accepted favors acceptance, and certain modalities are prepotent over others, as hearing versus vision or touch versus temperature in the dog. (Some constant relations, as pitch and laterality, are reflected in auditory cortex potentials, according to Ades.) On the side of the organism, the presence of a particular 'drive state' favors selection of events related to its reinforcement (satisfaction)—a hungry animal attends to food. Further, experience is stored, in the sense that the probability of one selected signal following another helps determine future selection; conditioning can alert or habituate attention.

Perhaps more exciting than the preceding more formal statements of common experience is evidence that incoming information may be held in temporary storage for seconds before passing through the limited capacity channel, along with other events of the same class. The duration of temporary storage can be increased beyond this short time by passing the information through the limited capacity channel and returning it to temporary storage, a cyclic process that can be continued for some time, but at the expense of using up part of the capacity. Long-term storage, by contrast, adjusts the internal coding to the probabilities of external events and does not encroach upon the dynamic communication channel. (Here again the neurophysiological picture of a dynamic memory, involving messages reverberating in closed neuron loops, and of a fixed memory, involving material changes in and altered physiological properties of such loops, is in congruence.)

Of especial interest is the conclusion that a shift from one class of events to another, in the selective process, requires a time of significant duration in relation to that for continuous flow of one class of events. (Bartley supplies evidence for afferent channels becoming refractory for 0.1 sec., with phasic filtering of visual, auditory and other inputs.) Attention 'blinks' or 'nods' while messages of one sort are received during which another type is transmitted. (This is based on studying the reception of conflicting auditory messages, but is reminiscent of the fading of pattern vision when jiggling of the retinal image is prevented, as described by Eldred and Whitteridge. Removal of the frontal intrinsic cortex leads to 'flickering' of attention, according to Pribram, which would relate the selective filter to this brain mechanism.) Finally, there is tentative evidence that information from one type of event is sampled for some minimal time before it results in action; decision waits upon some minimal accumulation of relevant data. (This would fit the suggestion of

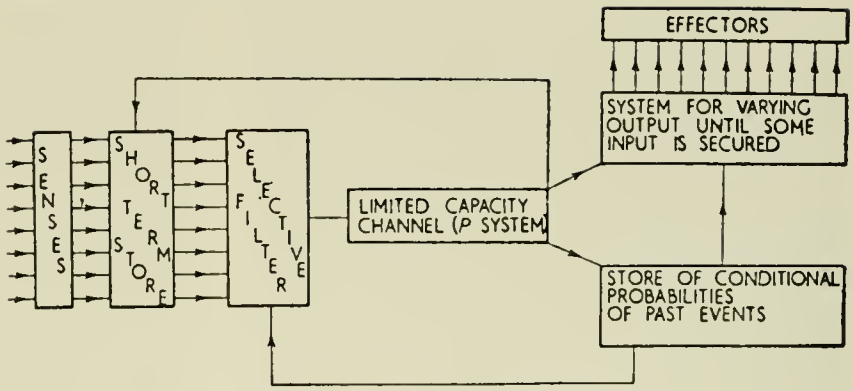



FIG. 2. Broadbent's information-flow diagram for the organism. For description see the text. [From Broadbent (32).]

reverberation prior to perception and that of temporal integration at the synaptic decision points.)

Figure 2, Broadbent's information-flow diagram for the organism, covers research by himself and others on immediate memory, on learning, on anticipation and refractoriness, and on noise, multichannel listening and prolonged performance. It is obvious that this model, reached exclusively from studies of behavior of intact organisms, mainly man, is subject to easy translation into a neurophysiological model, based on direct manipulation of the nervous system of animals.[5]

### *An Action Wave Model*

An especially impressive model has been offered by Beurle (24) who starts with assumptions based upon reasonable neurophysiological knowledge, develops from these a formal model, and demonstrates as mathematical consequences a set of behavioral properties that parallel many facets of complex human behavior. It will be interesting to present first a summary of Beurle's formulation and then to marshall some of the material in this *Handbook* that fits in with and supports it.

FORMULATION. *Waves in a neuron mass.* Assume a population of neurons, the cells distributed randomly in a mass and making random connections with other cells, except that connections with others decrease as some, not critical, function of the distance between them. Impulses travel from cell to cell along the connections and a given cell fires when a sufficient number of connections, about 10 assumed, sum their activities. A brief synaptic delay intervenes between effective summation and discharge. After a cell has been fired ('used'), it will remain inactive for a time and, aside from such a 'refractory period,' its threshold will remain constant or, on later assumptions, will be lowered cumulatively by previous activity and will be temporarily raised by inhibitory or lowered by excitatory connections. A wave entering such a cell mass does not spread from cell to cell, as in simple chains, and need not activate all cells as it travels; rather propagation requires the convergence of many cell influences on each, and the divergence of each cell's influence on many; and the spread of the wave is nonlinear in relation to excitation level and cell thresholds.

A wave front of active cells at time, $t$, advances during the time increment, $\tau$, by activating additional cells in front of it. The proportion ($F$) of the cells in any cross-section that become active as the wave passes through it will remain constant—$F_{t+\tau} = F_{(t)}$—only for a critical initial value of $F$, $F_0$. Above this level, activity rises to a saturation of active cells; below this, the wave decrements to extinction.

[5] Beurle writes me [see also Beurle (25)] on the fit of his model (below) with Broadbent's as follows:

"It is easy to conceive a reverberatory store arising out of a network in which there is a large random factor, but the problem is that there would be a random relationship between the output and the information stored. This is very easily solved if the output from the reverberatory store is fed directly to the input of my original model since this latter is essentially capable of dealing with, and sorting out, information arriving along a set of randomly connected fibres.

"The combination of short term memory with the original long term memory model would go far towards explaining many of the well known features of our memory. It would explain our ability to 'telescope' the time scale of past events so that when we recall a train of memories it is only the important highlights that come back. It would also explain how single, but important events can often be remembered well, a fact that is less easy to account for on a basis of the original simple long term memory model alone."

Clearly, therefore, without additional regulation there can be no uniform maintained cell activity nor regular waves traveling through the mass. Waves could arise here and there from active foci and either spread a way before dying out or rise to maximal intensity and spread indefinitely (convulsive or ictal activity). Beurle later notes (personal communication) that inhibitory components are essential for stability. The wave will decrement or increment sharply, to time units (10τ) will suffice for it to rise to saturation, or fall to zero, if the threshold is, respectively, only one per cent above, or below, the critical value.

Since used cells lie in the wake of a wave front, there are always more sensitive cells ahead than behind, and the wave passes forward as a true excitation wave. The used cells recover, however, so saturated waves can recur at a frequency determined by the recovery period, and unsaturated ones can recur even faster. Waves can thus return to or even cross in a given region. Moreover, since only some cells are used by unsaturated waves, each wave engaging its own unique set, waves of the same size and course can travel through the same cell mass and yet differ in detail in the actual cells used, and so possess individual identities. The detailed shape and movement of a wave would depend, further, on the actual shape of the cell mass. A wave originating at a point would tend to spread spherically in a homogeneous mass; but on reaching the surfaces of a sheet, it would continue to spread in it as a cylindrical or linear wave front. Clearly, for such activity a thick flat cortex would be far from equivalent to a thin convoluted one.

*Controls.* If a special set of excitatory (E) axons penetrated the cell mass, each able to contribute a partial pre-excitation of cells in the mass, a traveling wave would be facilitated when such axons were active. Comparably, a set of inhibitory (I) fibers which would predischarge a few neurons (or a subset of I cells, especially easily discharged) would reduce the density of responsive cells and so tend to inhibit a wave. Even simpler, I fibers may directly inhibit, aside from predischarge of cells, an assumption Beurle was earlier advised to eschew but now prefers (personal communication). Either or both mechanisms would suffice for regulation; the situation is symmetrical. Finally, with a set of axons from the main cell mass to the special E or I cells, acting as a servo or feed-back control, a wave could be stabilized so that it would travel through the mass at some constant value well below saturation. Such a wave, now entering a cell region where travel is more difficult, will progressively attenuate until only one final cell is stimulated after the wave penetrates some distance into the region. But, since each wave is specific in the neurons it uses, even though all waves are of the same total size, each will activate a different terminal cell; in fact, which terminal cell is fired could serve to define the wave.

The point at which a wave arises clearly could correspond to input to a central mass; the terminal cell or area, to the output; and the region in which a controlled constant wave moves, to the cortex or to any other central nervous mass of neurons. If, now, the assumption is introduced that each activation leaves a minute lasting fall in the threshold of a cell, a given wave will pass through the neuron mass more easily each time it is evoked. Any other wave, even through the same total neuron population, will not be significantly enhanced, which easily accounts for discriminative learning.

All sensory messages reach the cell mass and can start waves. The further assumption of a discriminator, such that sensations which produce effects desirable to the organism activate E while those producing undesirable ones activate I, helps explain adaptive learning. In a familiar environment, with usual inputs, waves will travel along established facilitated 'paths' and give the usual motor responses. In a new environment, with novel excitation, new waves will travel, a new motor unit be reached and some different act follow. If this leads to satisfactory results, so producing a desired input, 'E' will be activated; the wave will be reinforced for future travel; and the response, 'learned.' If the result is unsatisfactory, 'I' will be activated; the wave will be blocked or deflected to a different output cell; and the 'trial and error' behavior will continue until a satisfactory response is obtained. Since the presence of a goal normally is implicit to the very process of learning, the only real assumption here is as to the mechanism of the E or I effects.

*Reactivation properties.* The model has further richness, without additional assumptions. The regulated wave, controlled by a feed-back circuit which has a time lag, can reflect from the boundary of a region of difficult travel—one with a lower cell density or higher cell thresholds. Two waves can cross without dying out; since activation is nonlinear, the proportion of cells active will be more than doubled where the waves meet. Best of all, waves meeting at an angle will form a line of the loci of crossing of the advancing wave fronts, a line at which excitation was excessive. The cells in this track of the crossing point

would have their thresholds lowered and, on sufficient repetition, would constitute an enduring low-threshold path—the structural engram demanded by each memory. A new wave of either of the initial types, but no other kind of wave, on reaching this low threshold region could set up the other initial wave type or could reflect back on itself—a mechanism for conditioning. Even more generally, two waves present in a region could 'recruit' cells not activated by either but which would then link both—a diffuse engram and a conditioning mechanism (Beurle, personal communication). Finally, if a last assumption be made that some recurrent fibers from the output of the mass can bring excitation back to the input region, recurrent waves could travel through the mass and so different outputs be 'explored.' This model thus accounts for reason based on memory and imagery, and can choose the 'good' response internally rather than by behavioral trial and error.

EPITOME. For comparison with further neurophysiological data, it will be convenient to epitomize the model as follows. *a*) Given a random mass of neurons with random connections, waves will arise in it, will decrement or increment as they spread, and, in the latter case, will be able to retravel a given region. *b*) If special sets of cells send excitatory (E) or inhibitory (I) axons into the mass and if axons from the mass act upon these sets so as to constitute a negative feed-back system, then constant waves can travel through the mass; and different waves can travel in the same mass, using different actual cell patterns, leaving different traces, reaching different end cells, and in general retaining individuality. *c*) Activity lowers excitation threshold; a given wave traversing the cell mass will thus favor the subsequent passage of that wave but of no other. *d*) An input favorable to the organism activates E and therefore facilitates the passage of the associated wave; an unfavorable one activates I and so deflects the wave into new paths and to a new output. *e*) Waves kept at a constant level by the servomechanism of (*b*) can reflect from a region of difficult propagation, can cross one another, can leave enduring low threshold tracks where wave fronts have once crossed, and can regenerate themselves or others which have crossed them from this locus. More diffuse low-threshold cell groups can similarly form and later regenerate paired waves. *f*) With a final assumption, of recurrent connections from the output of such a mass to the input, recurrent waves can travel, the effects of a presumptive output can be sampled and problems can be solved by reason rather than by behavioral trial and error.

EXPERIMENTAL SUPPORT. A random population with random connections is a weak postulate; any additional structuring must give richer attributes. Indeed, a powerful approach to the actual table of organization (or sociometrics!) of neurons is offered by the departure of the system from that of a random net (239). A good example of the specific and the probabilistic connections is given by the spread of myotatic responses, both to well-channeled effector outlets and to others, as a function of distance from the input locus (Lloyd). The tendency of a wave to fade out or to rise to a maximum is reminiscent of the local excitatory process in nerve (156) and has also been urged for cell masses (71) as well as for explosive summation in cord and brain (Bartley).

That feed-back modulating mechanisms operate on neural masses is hardly a postulate. Both excitatory and inhibitory inflows to the cortex exist, as from the reticular formation and from the cerebellum; and both E and I influences from each of these centers play downstream, and the proportion of E and I output, for example from the cerebellum, in turn is modulated by the rate of input to this high-frequency synchronously-discharging organ (Brookhart). Volleys to the cortex via the nonspecific system sensitize the deep cells to volleys via the specific one, and they help control the timing and gating of cortical neuron discharges, including spread within the cortex (Jasper). These actions are associated with dendritic potentials and presumably influence soma threshold in the expected manner (Jasper, Chang). With learning, electrical responses appear in deep structures (especially the hypothalamus) before the cortex, and stimulation of these (especially the centromedian nucleus) can speed conditioning manyfold (20). Certainly waves of potential change of constant amplitude can sweep across the mammalian cortex (167, 179) and the amphibian forebrain (174).

There is also some evidence that different waves can traverse the same neuron population. Changing the parameters, such as the frequency of stimulation to a given locus [medulla (56, 298), thalamus (5), cerebellum (214)], can lead to quite different outputs. Different sequences of complex motor acts are elicited from nearby cerebellar regions despite their rich neuronal linkage and joint participation in the process (Brookhart). A given neuron can be made to fire at a higher or lower frequency by the same vestibular stimulation, depending on head position

(Gernandt); and a given stimulus will lead to extension of a flexed leg, flexion of an extended one (268). Indeed, the ability to use the same muscle groups in a variety of coordinated acts, including highly specialized learned skills, is almost a restatement of the ability of a neural mass to transmit many independent activation patterns.

It is not necessary again to marshall evidence that activity leaves behind some lowering of thresholds and, therefore, makes learning possible; but it is worth noting that feed-back controls into a mass of neurons could themselves influence the amount and locus of reverberating activity and so the character of enduring traces. Thus the influence of limbic and brain-stem structures on recent memory is easily understood. That 'good' outcomes reinforce behavior and 'bad' ones extinguish it is solidly established, and that particular brain regions are concerned in this is becoming apparent. The frontal intrinsic area gives direction and continuity to behavior (Pribram), much as the discriminator postulated by Beurle. Frontal temporal lesions are associated with loss of signs of affect (MacLean), and lesions near the third ventricle or of the cingulate gyrus may eliminate 'willing' (French). The whole question of attention is obviously related and Livingston clearly states the view that the channeling of pathways by positive reinforcement is the basis of values.

Some direct evidence favors Beurle's theoretical conclusion that where two waves meet the amount of excitation is increased and may be more than doubled. This is, in fact, the phenomenon of spatial summation and subliminal fringe. It is exemplified by the ability of a double maximal shock to the optic nerve to produce a supermaximal response in the geniculate (Bartley), time presumably being translated into space. The regions of low threshold established by repeated action of certain waves, the engrams, constitute the internalized patterns derived from and representing the external world (49) and also constitute the encoded programs for behavior (Pribram). It is highly relevant that evoked potentials in the auditory cortex can trigger spontaneous waves of the Lilly type (Ades), and that cortex waves do slow at area boundaries (179), just as predicted by the model.

The final assumption, of internal feedback from output to input, is at least suggested by the phenomena of conditioning via direct stimulation of the cortex, with no sensory input or observable behavioral output in the process (Galambos & Morgan). While a motor skill is being acquired, at first visual feedback is most important but later proprioceptive information dominates (Paillard). One can 'feel' oneself performing a skilled act and accomplished musicians 'practice' playing a composition without moving a muscle, and with a consequent improvement in performance, by 'felt' motor and proprioceptive experiences. Similarly, linguists (140) postulate an ongoing emission of internal language from a 'marshalling yard' of words and grammar, and a continuous feedback into it of such verbal activity—with internal editing—the equivalent of E and I control of repeating in a neuron mass. In conditioning, cortical potential responses appear before motor behavioral responses, and they endure longer during extinction (20, 21). (Less clear is the falling out of cortex responses, with retention of motor ones, in sleep and habituation.)

Such a model, built upon and supported by sound neurophysiology, comes encouragingly close to offering a workable and satisfying picture of neural mechanisms of behavior. Thus, at the neuron and neuron-group levels, neurophysiology and general psychology are joining hands, just as, at the molecular and organelle levels, biochemistry and general physiology are doing likewise.

## CLOSE

Man's large and organized brain has enabled him to receive and process information to an unparalleled degree and, on the basis of this, to manipulate and control his environment with great potency. Highly structured communication between men, involving the classification of experience, the distillation of concepts from this and their formalization into a coded language made possible the collective creation of tools and machines, of fire and other energy sources, of structures for habitation and production and movement, of the institutions and aspirations of a community, of the whole rich synthetic environment of culture in which all civilized men are immersed.

Mankind, operating in groups and societies, as higher level systems or epiorganisms, has become the great catalyst of evolution. Man, as all living things, has consumed energy to decrease entropy and create order or information. Man's numbers, his institutions, his records and his knowledge are all increasing along exponential curves. The latter, due to science, has the shortest time constant, doubling every 15 years since science began two and a half centuries ago (233).

Truly, man is the highest organism, with an exquisite instrument for communication and invention. From study of the brain will flow great advances in behavioral science. Perhaps with inventions to enhance man's reasoning and valuing processes (and so to improve the patterns and skills of social interactions), comparable to the power machines that supplement his muscles and the detecting instruments that extend his senses, we shall learn to live with ourselves and with others before it is too late.

## REFERENCES

As noted in the opening footnote, this bibliography is selective and impressionistic. It contains references to new or peripheral material and to articles omitted from or of special relevance in the Handbook chapters. The great bulk of neurophysiological literature is, of course, covered in the chapters. These chapters, rather than the specific articles reviewed in them, are cited freely in the text of this summary chapter. Such references are easily recognized by the absence of a number following the name of the chapter author. Other references are numbered.


1. Abood, L. G. and R. W. Gerard. A phosphorylation defect in the brains of mice susceptible to audiogenic seizures. In: *Biochemistry of the Developing Nervous System*, edited by H. Waelsch. New York: Acad. Press, 1955, p. 467.
2. Adey, W. R. Organization of the rhinencephalon. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 621.
3. Adey, W. R. Paper presented at the Symposium on *Brain Mechanisms and Learning*, Montevideo, 1959. In preparation.
4. Adey, W. R., C. W. Dunlop, K. F. Killam and M. A. B. Brazier. Investigations of the action of thiosemicarbazide on the cerebellar cortex of the cat. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
5. Akimoto, H. and O. Creutzfeldt. *Arch. Psychiat.* 196: 520, 1958.
6. Albe, D. *Compt. rend. Soc. de biol.* 135: 1563, 1941.
7. Allanson, J. T. Some properties of a randomly connected neural network. In: *Information Theory*, edited by C. Cherry. New York: Acad. Press, 1956, p. 303.
8. Alonso-deFlorida, F. and J. M. R. Delgado. *Am. J. Physiol.* 193: 223, 1958.
9. Alt, F. L. *Electronic Digital Computers*. New York: Acad. Press, 1958.
10. Arduini, A. Lasting potential changes evoked in the cerebral cortex by stimulation of brain stem reticular formation and thalamus. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 333.
11. Arieti, S. *Interpretation of Schizophrenia*. New York: Brunner, 1955.
12. Ashby, W. R. *Design for a Brain*. New York: Wiley, 1952.
13. Ashby, W. R. *An Introduction to Cybernetics*. New York: Wiley, 1956.
14. Bales, R. F. *Interaction Process Analysis. A Method for the Study of Small Groups*. Cambridge: Addison-Wesley, 1951.
15. Barlow, H. B. Sensory mechanisms, the reduction of redundancy, and intelligence. In: *Symposium on the Mechanization of Thought Processes*. National Physical Laboratory Symposia, No. 10. London: Her Majesty's Stat. Off. 1959.
    Laboratory, Teddington, Middlesex, England. In press.
16. Barlow, J. S. and M. A. B. Brazier. *Electroencephalog. & Clin. Neurophysiol.* 6: 321, 1954.
17. Bates, J. A. V. *J. Physiol.* 113: 240, 1951.
18. Bateson, G., D. D. Jackson, J. Haley and J. Weakland. *Behav. Sci.* 1: 251, 1956.
19. Bavelas, A. Communication patterns in problem-solving groups. In: *Cybernetics*, edited by H. von Foerster. New York: Macy, 1951, p. 1.
20. Beck, E. C. Paper presented at Sixth Research Institute on Clinical Psychology: *Brain Function and Personality*, Univ. of Kansas, 1959. To be published.
21. Beck, E. C., R. W. Doty and K. A. Kooi. *Electroencephalog. & Clin. Neurophysiol.* 141: 279, 1958.
22. Berkeley, E. C. *Giant Brains*. New York: Wiley, 1949.
23. Bessman, S. P. and K. Tada. *Pediatrics* 23: 1004, 1959.
24. Beurle, R. L. *Phil. Trans. B* 240: 55, 1957.
25. Beurle, R. L. *J. Inst. Elect. Engrs. (London)* 5: 75, 1959.
26. Bickford, R. G., D. W. Mulder, A. W. Dodge, Jr., H. J. Svien and H. P. Rome. *A. Res. Nerv. & Ment. Dis., Proc.* 36: 227, 1958.
27. Bishop, G. H. *Electroencephalog. & Clin. Neurophysiol.* 10, Suppl. 10: 12, 1958.
28. Boszermenyi-Nagy, I. and F. J. Gerty. *Confinia neurol.* 18: 92, 1958.
29. Bremer, F. *Physiol. Rev.* 38: 357, 1958.
30. Brickner, R. *Tr. Am. Neurol. A.* 65: 189, 1939.
31. Brink, F. Excitation and conduction in the neurone. In: *Handbook of Experimental Psychology*, edited by S. S. Stevens. New York: Wiley, 1951, p. 50.
32. Broadbent, D. E. *Perception and Communication*. New York: Pergamon Press, 1958.
33. Bronowski, J. *Science and Human Values*. New York: Messner, 1958.
34. Brooks, V. B., R. E. Ransmeier and R. W. Gerard. *Am. J. Physiol.* 157: 299, 1949.
35. Bruner, J. S. *A. Res. Nerv. & Ment. Dis., Proc.* 36: 118, 1958.
36. Bullock, T. H. *Science* 129: 997, 1959.
37. Bullock, T. H. and C. A. Terzuolo. *J. Physiol.* 138: 341, 1957.
38. Bureš, J., O. Burešova and A. Záharová. *J. Comp. & Physiol. Psychol.* 51: 263, 1957.
39. Burns, B. D. *The Mammalian Cerebral Cortex*. Baltimore: Williams & Wilkins, 1958.

40. Callaway, E., III, and D. Dembro. *A.M.A. Arch. Neurol. & Psychiat.* 79: 74, 1958.
41. Cheek, D. B. *Am. J. Clin. Hypnosis* 1: 101, 1959.
42. Chow, K. L. and E. R. John. *Science* 128: 781, 1958.
43. Christie, L. S. and R. D. Luce. *Bull. Math. Biophys.* 18: 89, 1956.
44. Clynes, M. The mathematical law of the respiratory heart rate reflex (RHR) in man. In: *Medical Physics*, edited by O. Glasser. Chicago: Yr. Bk. Pub., 1960, vol. 3.
45. Coghill, G. E. *Anatomy and the Problem of Behavior.* London: Cambridge, 1929.
46. Colby, K. M. *Energy and Structure in Psychoanalysis.* New York: Ronald, 1955.
47. Cole, J. O. and R. W. Gerard (editors). *Psychopharmacology: Problems in Evaluation.* Nat. Acad. Sc.-Nat. Res. Council Publ. 583, Washington, 1959.
48. Coursin, D. B. Seizures in vitamin $B_6$ deficiency. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
49. Craik, K. J. W. *The Nature of Explanation.* London: Cambridge, 1943.
50. Creutzfeldt, O. and H. Akimoto. *Arch. Psychiat.* 196: 520, 1958.
51. Culbertson, J. T. *Consciousness and Behavior: A Neural Analysis of Behavior and Consciousness.* Dubuque, Iowa: Brown, 1950.
52. Culbertson, J. T. *The Minds of Robots.* In preparation.
53. Curtis, D. R. and J. C. Watkins. Investigations upon the possible synaptic transmitter function of gamma-aminobutyric acid and naturally occurring amino acids. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
54. Dell, P. C. Humoral effects on the brain stem reticular formation. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 365.
55. Detwiler, S. R. *Neuroembryology: An Experimental Study.* New York: Macmillan, 1936.
56. Doty, R. W. *Am. J. Physiol.* 166: 142, 1951.
57. Doty R. W. Conditioned reflexes formed and evoked by brain stimulation. In: *Electrical Stimulation of the Brain*, edited by D. E. Sheer. Austin: Univ. Texas Press. In press.
58. Doty, R. W. and R. W. Gerard. *Am. J. Physiol.* 162: 458, 1950.
59. Downer, J. L. DeC. *Fed. Proc.* 17: 37, 1958.
60. Dubner, H. H. and R. W. Gerard. *J. Neurophysiol.* 2: 142, 1939.
61. Duncan, C. P. *J. Comp. & Physiol. Psychol.* 42: 32, 1948.
62. Eccles, J. C. *The Neurophysiological Basis of Mind.* Oxford: Clarendon Press, 1953.
63. Edisen, A. E. *Am. J. Physiol.* 184: 223, 1956.
64. Edwards, C. Physiology and pharmacology of the crayfish stretch receptor. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
65. Elkes, J. Schizophrenic process in relation to levels of neural organization. The need for some conceptual points of reference. In: *The Chemical Pathology of the Nervous System*, edited by J. Folch-Pi. New York: Pergamon Press. In press.
66. Emerson, A. E. *Scient. Month.* 78: 67, 1954.
67. Evarts, E. V. A discussion of the relevance of effects of drugs on animal behavior to the possible effects of drugs on psychopathological processes in man. In: *Psychopharmacology: Problems in Evaluation*, edited by J. O. Cole and R. W. Gerard. Nat. Acad. Sc.-Nat. Res. Council Publ. 583, Washington, 1959, p. 284.
68. Fankhauser, G., J. A. Vernon, W. H. Frank and W. V. Slack. *Science* 122: 692, 1955.
69. Farrell, G. L. *Recent Progr. Hormone Res.* 15: 275, 1959.
70. Fatt, P. Alterations produced in the post-junctional cell by the inhibitory transmitter. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
71. Fessard, A. Mechanisms of nervous integration and conscious experience. In: *Brain Mechanisms and Consciousness*, edited by E. D. Adrian, F. Bremer, H. H. Jasper and J. F. Delafresnaye. Springfield: Thomas, 1954.
72. Fessard, A. Les mécanismes de synchronisation interneuronique et leur intervention dans la crise épileptique. In: *Bases Psychologiques et Aspects Cliniques de l'Épilepsie.* Paris: Masson, 1958, p. 37.
73. Fitts, P. M., H. Bahrick, M. Noble and G. A. Briggs. *Skilled Performance.* New York: Wiley. In press.
74. Folch-Pi, J. (editor). *The Chemical Pathology of the Nervous System.* New York: Pergamon Press. In press.
75. Gammon, G. D. Studies of the action of convulsant hydrazides as vitamin $B_6$ antagonists in the central nervous system. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
76. Gantt, W. A. H. (editor). *Physiological Bases of Psychiatry.* Springfield: Thomas, 1958.
77. Garcia-Austt, E. Paper presented at the Symposium on *Brain Mechanisms and Learning*, Montevideo, 1959. In preparation.
78. Geiger, A. *Physiol. Rev.* 38: 1, 1958.
79. Geiger, R. S. *In vitro* studies on the growth properties of brain cortex cells of adult individuals. In: *Ultrastructure and Cellular Chemistry of Neural Tissue*, edited by H. Waelsch. New York: Hoeber, 1957, p. 83.
80. Gellhorn, E. *Autonomic Imbalance and the Hypothalamus.* Minneapolis: Univ. Minnesota Press, 1957.
81. George, F. H. *Science* 127: 1269, 1958.
82. Gerard, R. W. *Quart. Rev. Biol.* 6: 59, 1931.
83. Gerard, R. W. *Physiol. Rev.* 12: 469, 1932.
84. Gerard, R. W. *Cold Spring Harbor Symp. Quant. Biol.* 4: 194, 1936.
85. Gerard, R. W. *A. Res. Nerv. & Ment. Dis., Proc.* 18: 316, 1937.
86. Gerard, R. W. *Ann. Rev. Biochem.* 6: 419, 1937.
87. Gerard, R. W. *Scient. Month.* 44: 48, 1937.
88. Gerard, R. W. *A.M.A. Arch. Neurol. & Psychiat.* 40: 985, 1938.
89. Gerard, R. W. *Ohio J. Sci.* 41: 160, 1941.
90. Gerard, R. W. *Philos. of Sc.* 9: 92, 1942.
91. Gerard, R. W. *Ann. Rev. Physiol.* 4: 329, 1942.
92. Gerard, R. W. *Biol. Symp.* 8: 67, 1942.
93. Gerard, R. W. *Ethics* 56: 219, 1946.
94. Gerard, R. W. *Scient. Month.* 62: 477, 1946.
95. Gerard, R. W. *Ann. New York Acad. Sc.* 47: 575, 1946.
96. Gerard, R. W. *Electroencephalog. & Clin. Neurophysiol.* 1: 53, 1949.

97. Gerard, R. W. *Am. J. Psychiat.* 106: 161, 1949.
98. Gerard, R. W. Some of the problems concerning digital notions in the central nervous system. In: *Cybernetics*, edited by H. von Foerster. New York: Macy, 1950, p. 11.
99. Gerard, R. W. *Common Cause* 3: 630, 1950.
100. Gerard, R. W. *Recent Progr. Hormone Res.* 5: 37, 1950.
101. Gerard, R. W. *Anesthesiology* 12: 1, 1951.
102. Gerard, R. W. *Scient. Month.* 189: 118, 1953.
103. Gerard, R. W. *Pharmacol. Rev.* 6: 123, 1954.
104. Gerard, R. W. *Science* 120: 727, 1954.
105. Gerard, R. W. *Science* 122: 225, 1955.
106. Gerard, R. W. Metabolism and function in the nervous system. In: *Neurochemistry*, edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield: Thomas, 1955, p. 458.
107. Gerard, R. W. *Ann. New York Acad. Sc.* 67: 885, 1957.
108. Gerard, R. W. Summary. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 745.
109. Gerard, R. W. *Bull. New York Acad. Med.* 34: 429, 1958.
110. Gerard, R. W. *Behav. Sci.* 3: 92, 1958.
111. Gerard, R. W. *Dis. Nerv. System* Monogr. Suppl. 20: 33, 1959.
112. Gerard, R. W. *Human Biol.* 31: 14, 1959.
113. Gerard, R. W. Aging and organization of behavior. In: *Handbook of Aging and the Individual*, edited by J. E. Birren. Chicago: Univ. Chicago Press, 1959.
114. Gerard, R. W. Neurophysiology: Brain and Behavior. In: *American Handbook of Psychiatry*, edited by S. Arieti. New York: Basic, 1959, p. 1620.
115. Gerard, R. W. The architecture of knowledge and neural function. In: *Symposium on Experimental Psychiatry*, edited by H. W. Brosin. In preparation.
116. Gerard, R. W. Summary. In: *Stress and Psychiatric Disorder*, edited by J. M. Tanner. Oxford: Blackwell. In press.
117. Gerard, R. W. The brain: mechanism of the mind. In: *An Outline of Man's Knowledge of the Modern World*, edited by L. Bryson. New York: McGraw-Hill, 1960, p. 73.
118. Gerard, R. W. and B. Libet. *Am. J. Psychiat.* 96: 1125, 1940.
119. Gerard, R. W. and B. Libet. General neurophysiology. In: *Progress in Neurology and Psychiatry*, edited by S. Spiegel. New York: Grune, 1946.
120. Gerard, R. W. and H. W. Magoun. *Proc. Soc. Exper. Biol. & Med.* 34: 755, 1936.
121. Gerard, R. W., W. H. Marshall and L. J. Saul. *A.M.A. Arch. Neurol. & Psychiat.* 36: 675, 1936.
122. Gerschenfeld, H. M., F. Wald, J. A. Zadunaisky and E. D. P. de Robertis. *Neurology* 9: 412, 1959.
123. Gottlieb, J. S., C. E. Frohman, P. G. S. Beckett, G. Tourney and R. Senf. *A.M.A. Arch. Gen. Psychiat.* 1: 243, 1959.
124. Gottlieb, J. S., C. E. Frohman, G. Tourney and P. G. S. Beckett. *A.M.A. Arch. Neurol. & Psychiat.* 81: 504, 1959.
125. Granit, R. *Receptors and Sensory Perception.* New Haven: Yale Univ. Press, 1955.
126. Grastyan, A. The hippocampus and nervous activity. In: *Central Nervous System and Behavior*, edited by M. A. B. Brazier. New York: Macy, 1959, p. 119.
127. Green, B. F., Jr. *Behav. Sci.* 4: 164, 1959.
128. Grundfest, H. *Electroencephalog. & Clin. Neurophysiol.* 10, Suppl. 10: 22, 1958.
129. Haber, C. and L. Saidel. *Fed. Proc.* 7: 47, 1948.
130. Hagbarth, K. E. and J. Fex. *J. Neurophysiol.* 22: 321, 1959.
131. Harary, F. and R. Z. Norman. *Graph Theory as a Mathematical Model in Social Science.* Ann Arbor: Inst. Social Res., 1953.
132. Harlow, H. F. Behavioral contributions of interdisciplinary research. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 3.
133. Hebb, D. O. *The Organization of Behavior.* New York: Wiley, 1949.
134. Hebb, D. O. *Psychol. Rev.* 62: 243, 1955.
135. Hebb, D. O. Alice in Wonderland, or psychology among the biological sciences. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 451.
136. Hess, W. R. In: *The Functional Organization of the Diencephalon*, edited by J. R. Hughes. New York: Grune, 1958.
137. Hick, W. E. *Trans. Soc. Instrum. Techn.* 4: 67, 1952.
138. Hill, S. E. *Am. J. Physiol.* 126: 534P, 1939.
139. Himwich, H. E. *Brain Metabolism and Cerebral Disorders.* Baltimore: Williams & Wilkins, 1951.
140. Hockett, C. F. *Internat. J. Am. Linguistics* 21: Suppl., 1955.
141. Hodgkin, A. L. *Proc. Roy. Soc., London, ser. B* 148: 1, 1958.
142. Hooker, D. *The Prenatal Origins of Behavior.* Lawrence: Univ. Kansas Press, 1952.
143. Hume, D. M. Hypothalamic localization for the control of various endocrine secretions. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 231.
144. Huxley, A. *Ann. New York Acad. Sc.* 67: 675, 1957.
145. Hyden, H. Biochemical changes in glia cells and nerve cells at varying activity. In: *Biochemistry of the Central Nervous System*, edited by F. Brucke. New York: Pergamon Press, 1959, vol. III.
146. Jackson, D. D. *The Etiology of Schizophrenia.* New York: Basic. In press.
147. Jasper, H. H. Reticular-cortical systems and theories of the integrative action of the brain. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 37.
148. Jasper, H. H. Current concepts of nervous inhibition. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
149. Jasper, H. H., L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello (editors). *Reticular Formation of the Brain.* Boston: Little, 1958.
150. Jenerick, H. P. and R. W. Gerard. *J. Comp. & Physiol. Psychol.* 42: 79, 1953.
151. John, L. R. and K. F. Killam. *J. Pharmacol. & Exper. Therap.* 125: 252, 1959.
152. John, E. R. and K. F. Killam. *J. Nerv. & Ment. Dis.* In press.
153. Jung, R. Coordination of specific and nonspecific afferent impulses at single neurones of the visual cortex. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 423.
154. Kallmann, F. J. Genetic aspects of psychoses. In: *Biology*

*of Mental Health and Disease*. New York: Hoeber, 1952, p. 283.
155. Kallmann, F. J. *J. Ment. Sc.* 104: 549, 1958.
156. Katz, B. *Electric Excitation of Nerve*. London: Oxford, 1939.
157. Kety, S. S. *Science* 129: 1528, 1590, 1959.
158. Killam, E. K. and K. F. Killam. Pharmacological studies of evoked cortical potentials. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
159. Kleitman, N. *Sleep and Wakefulness*. Chicago: Univ. Chicago Press, 1939.
160. Köhler, W. and H. Wallach. *Proc. Am. Philos. Soc.* 88: 269, 1944.
161. Korey, S. R. and J. I. Nurnberger (editors). *Progress in Neurobiology. 3. Psychopharmacology*. New York: Hoeber-Harper, 1958.
162. Krech, D., M. R. Rosenzweig, E. L. Bennett and B. Krueckel. *Science* 120: 994, 1954.
163. Kreps, E. M. Quoted by Palladine and Vladimirov (228).
164. Kruse, H. D. (editor). *Integrating the Approaches to Mental Disease*. New York: Harper, 1957.
165. Lambert, W. E. and S. Fillenbaum. *Canad. J. Psychol.* 13: 28, 1959.
166. Land, E. H. *Proc. Nat. Acad. Sc., Washington* 45: 115, 1959.
167. Leão, A. A. P. *J. Neurophysiol.* 1: 359, 1944.
168. Leão, A. A. P. *Electroencephalog. & Clin. Neurophysiol.* 3: 315, 1951.
169. Ledley, R. S. and L. B. Lusted. *Science* 130: 9, 1959.
170. Lettvin, J. Y. and H. R. Maturana. *Mass. Inst. Technol., Research Lab. Electronics, Quart. Progr. Rep.* 53: 191, 1959.
171. Leukel, F. A. *J. Comp. & Physiol. Psychol.* 50: 300, 1957.
172. Lhemon, W. T. and S. Goldstone. *A.M.A. Arch. Neurol. & Psychiat.* 76: 625, 1956.
173. Li, C-L. and S. N. Chou. Inhibitory interneurons in the neocortex. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
174. Libet, B. and R. W. Gerard. *J. Neurophysiol.* 2: 153, 1939.
175. Libet, B. and R. W. Gerard. *J. Neurophysiol.* 4: 438, 1941.
176. Libet, B. and J. B. Kahn, Jr. *Fed. Proc.* 6: 152, 1941.
177. Licklider, J. C. R. The manner in which and extent to which speech can be distorted and remain intelligible. In: *Cybernetics*, edited by H. von Foerster. New York: Macy, 1951, p. 58.
178. Liddell, H. S. *Emotional Hazards in Animals and Man*. Springfield: Thomas, 1956.
179. Lilly, J. C. Correlations between neurophysiological activity in the cortex and short-term behavior in the monkey. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 83.
180. Lindsley, D. B. The reticular system and perceptual discrimination. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 513.
181. Lindsley, D. B. and W. H. Emmons. *Science* 127: 1061, 1958.
182. Ling, G. *Fed. Proc.* 17: 98, 1958.
183. Livanov, M. N. and K. L. Polyakov. *Bull. Acad. Sci. U.S.S.R., Ser. Biol.* 3: 286, 1945.
184. Livingston, W. K. *Pain Mechanisms; a Physiologic Interpretation of Causalgia and Its Related States*. New York: Macmillan, 1943
185. Lloyd, D. P. C. *J. Neurophysiol.* 4: 525, 1941.
186. Lloyd, D. P. C. *J. Gen. Physiol.* 33: 147, 1949.
187. Lorente de Nó, R. *J. Neurophysiol.* 2: 402, 1939.
188. Lorente de Nó, R. and G. A. Condouris. *Proc. Nat. Acad. Sc., Washington* 45: 592, 1959.
189. Luce, R. D. *A Survey of the Theory of Selective Information and Some of Its Behavioral Applications*. New York: Bureau of Applied Social Research, Columbia Univ., 1954, Technical Report 8.
190. Mandler, G. *J. Exper. Psychol.* 47: 411, 1954.
191. March, J. G. and H. A. Simon. *Organizations*. New York: Wiley, 1958.
192. Marrazzi, A. S. *Science* 90: 251, 1939.
193. Marrazzi, A. S. *Exper. Cell Res.* Suppl. 5: 370, 1958.
194. Marrazzi, A. S. Report of Third Year, Veterans Administration Research Laboratories in Neuropsychiatry, Pittsburgh, 1959.
195. Mason, J. W. The central nervous system regulation of ACTH secretion. In: *Reticular Formation of the Brain*, edited by H. H Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 645.
196. Mason, J. W. *Am. J. Physiol.* 196: 44, 1959.
197. Matte-Blanco, I. *Internat. J. Psycho-Anal.* 40: 1, 1959.
198. McConnell, J. V., R. Jacobsen and D. P. Kimble. *Am. Psychologist* 13: 382, 1958.
199. McConnell, J. V., R. Jacobsen and D. M. Maynard. *Am. Psychologist* 14: 410, 1959.
200. McConnell, J. V. and R. Thompson. *J. Comp. & Physiol. Psychol.* 48: 65, 1955.
201. McCulloch, W. S. *Physiol. Rev.* 24: 390, 1944.
202. McCulloch, W. S. Why the mind is in the head. In: *Cerebral Mechanisms in Behavior*, edited by L. A. Jeffress. New York: Wiley, 1951, p. 42.
203. McCulloch, W. S. *Mass. Inst. Technol., Research Lab. Electronics, Quart. Rep.* Apr. 15, 1958, p. 118.
204. McCulloch, W. S. and W. Pitts. *Bull. Math. Biophys.* 5: 115, 1943.
205. McGeer, E. G. and P. L. McGeer. *J. Ment. Sc.* 105: 1, 1959.
206. Meister, R. K. *A Hypothesis Concerning the Function of the Occipital Alpha Rhythm in Vision* (Doctoral Thesis). Chicago: Univ. Chicago, 1951.
207. Meyer, D. R. Some psychological determinants of sparing and loss following damage to the brain. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 173.
208. Miller, G. A. *Psychol. Rev.* 63: 81, 1956.
209. Miller, G. A., E. Galanter and K. Pribram. *Plans and the Structure of Behavior*. In preparation.
210. Miller, J. G. *Unconsciousness*. New York: Wiley, 1942.
211. Miller, J. G. *Am. J. Psychiat.* 116: 695, 1960
212. Milner, P. M. *Psychol. Rev.* 64: 242, 1957.
213. Morrell, F. Paper presented at the symposium on *Brain Mechanisms and Learning*, Montevideo, 1959. In preparation.
214. Moruzzi, G. *Problems in Cerebellar Physiology*. Springfield: Thomas, 1950.
215. Nachmansohn, D. *Ann. New York Acad. Sc.* 47: 395, 1946.
216. Neff, W. D. and I. J. Diamond. The neural basis of auditory discrimination. In: *Biological and Biochemical*

*Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 101.
217. Nelson, P. G. *J. Cell. & Comp. Physiol.* 52: 127, 1958.
218. Newcomb, T. M. *Psychol. Rev.* 60: 393, 1953.
219. Newell, A., J. C. Shaw and H. A. Simon. *Psychol. Rev.* 65: 151, 1958.
220. Newell, A., J. C. Shaw and H. A. Simon. Report on a general problem solving program. In: *Information Processing, Proceedings of the International Conference on Information Processing*. New York: UNESCO Publ. Ctr., 1960.
221. Olds, J. Self-stimulation experiments and differential reward systems. In: *Reticular Formation of the Brain*, edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. Boston: Little, 1958, p. 671.
222. Olds, J. *Science* 127: 315, 1958.
223. Olds, J. Studies of neuropsychopharmacology by electrical and chemical manipulation of the brain in animals with chronically implanted electrodes. In: *Proc. First Internat. Symposium of Neuropsychopharmacology*, edited by P. B. Bradley and others. Amsterdam: Elsevier. In press.
224. Olds, J. and M. E. Olds. Interference and learning in paleocortical systems. Paper presented at the Symposium on *Brain Mechanisms and Learning*, Montevideo, 1959. In preparation.
225. O'Leary, J. L. *A.M.A. Arch. Neurol. & Psychiat.* 76: 175, 1956.
226. Örström, Ä. and O. Skaug. *Acta. psychiat. et neurol.* 25: 437, 1950.
227. Otis, L. S. and J. A. Cerf. *Am. Psychologist* 13: 419, 1958.
228. Palladine, A. V. and G. E. Vladimirov. The use of radioactive isotopes in the study of functional biochemistry of the brain. In: *Proceedings of the International Conference on the Peaceful Uses of Atomic Energy*. New York: United Nations, 1956, vol. 12, p. 402.
229. Paton, W. D. *Pharmacol. Rev.* 6: 59, 1954.
230. Pfeiffer, C. C. Vitamin $B_6$, seizures and cerebral levels of gamma-aminobutyric acid. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
231. Piaget, J. *Construction of Reality in the Child*. New York: Basic, 1954.
232. Pitts, W. and W. S. McCulloch. *Bull. Math. Biophys.* 9: 127, 1947.
233. Price, D. J. *Discovery* 17: 240, 1956.
234. Purpura, D. P., S. Berl, O. Gonzalez-Monteagudo and A. Wyatt. Brain amino acid changes during methoxypyridoxine-induced seizures (cat). In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
235. Quastler, H. *Information Theory in Psychology*. Glencoe, Ill.: Free Press, 1955.
236. Rabe, A. and R. W. Gerard. *Am. Psychologist* 14: 423, 1959
237 Ransmeier, R. L. *The Effects of Convulsion, Hypoxia, Hypothermia and Anaesthesia on Retention in the Hamster* (Doctoral Thesis) Chicago: Univ. Chicago, 1954
238 Ransmeier, R. E. and R. W. Gerard *Am. J. Physiol.* 179: 663, 1954
239 Rapoport, A. *Bull. Math. Biophys.* 13: 85, 1951
240. Rapoport, A. *Bull. Math. Biophys.* 14: 35, 1952.
241. Rapoport, A. *Behav. Sci.* 4 299, 1959.
242. Ratliff, F., W. H Miller and H K Hartline. *Ann. New York Acad. Sc.* 74: 210, 1958.
243. Richter, D. (editor). *Metabolism of the Nervous System*. London: Pergamon Press, 1957.
244. Richter, D. (editor). *Schizophrenia: Somatic Aspects*. New York: Macmillan, 1957.
245. Riesen, A. H. Plasticity of behavior: psychological aspects. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 425.
246. Rinkel, M. and H. Hinwich (editors). *Insulin Treatment in Psychiatry*. New York: Philos. Libr., 1959.
247. Roberts, E. Free amino acids of nervous tissue: some aspects of metabolism of gamma-aminobutyric acid. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
248. Roberts, E. (editor). *Inhibition in the Nervous System and Gamma-aminobutyric Acid*. New York: Pergamon Press. In press.
249. Rochester, N., J. H. Holland, L. H. Haibt and W. D. Duda. *IRE Trans. on Inform. Theory. IT-2*, 1956, no. 3, p. 80.
250. Rome, B. K. and A. C. Rome. *Leviathan. A Simulation of Behavioral Systems to Operate Dynamically on a Digital Computer*. Santa Monica, Calif.: Systems Development Corporation, 1959, Report 5P-50.
251. Rosen, F., R. J. Milholland and C. A. Nichol. Studies on the inhibition of L-glutamic acid decarboxylase *in vivo*. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
252. Rosenblatt, F. *The Perceptron: a Theory of Statistical Separability in Cognitive Systems*. Buffalo, N. Y.: Cornell Aeronautical Laboratory, Jan. 1958, Report No. VV-1196-G-1.
253. Rosenblueth, A., N. Wiener, W. Pitts and J. Garcia Ramos. *J. Cell. & Comp. Physiol.* 34: 173, 1949.
254. Rosenzweig, M. R., D. Krech and E. L. Bennett. Brain chemistry and adaptive behavior. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 387.
255. Rubin, L. S. *Psychol. Bull.* 56: 375, 1959.
256. Rusinov, V. S. An electrophysiological analysis of the connecting function in the cerebral cortex in the presence of a dominant region area. *XIX Internat. Physiol. Congr., Abstr.* 719, 1953.
257. Russell, W. R. *Brain, Memory, Learning*. Oxford: Clarendon Press, 1959.
258. Samuels, A., L. L. Boyarsky, R. W. Gerard, B. Libet and M. Brust. *Am. J. Physiol.* 164: 1, 1951.
259. Samuels, I. *Psychol. Bull.* 56: 1, 1959.
260. Schade, J. P. and C. F. Baxter. Maturational changes in cerebral cortex. I. Volume and surface determinations of nerve cell components. In. *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
261. Schilder, P. The image and appearance of the human body. *Psychol. Monogr.* No. 4, 1935.
262. Sheerer, M. and R. Reiff. *Memory and Hypnotic Age Regression*. New York. Internat. Univ. Press, 1959.
263. Sigg, L., S. Ochs and R. W. Gerard. *Am. J. Physiol.* 183: 419, 1955.

264. Simon, H. A. and A. Newell. *Soc. Sci. Res. Council Items* 12: 37, 1958.
265. Smithies, J. R. *Analysis of Perception*. London: Routledge, 1956.
266. Smithies, J. R. *Brain* 80: 393, 1957.
267. Smithies, J. R. *Nature, London* 179: 523, 1957.
268. Sperry, R. W. Physiological plasticity and brain circuit theory. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: Univ. Wisconsin Press, 1958, p. 401.
269. Stark, L. Vision: servoanalysis of the pupil reflex to light. In: *Medical Physics*, edited by O. Glasser. Chicago: Yr. Bk. Pub., 1959, vol. 3.
270. Stark, L. and F. Baker. *J. Neurophysiol.* 22: 156, 1959.
271. Starkweather, J. A. *Am. J. Psychol.* 69: 121, 1956.
272. Stroud, J. M. The fine structure of psychological time. In: *Information Theory in Psychology*, edited by E. Quastler. Glencoe, Ill.: Free Press, 1955, p. 174.
273. Sugar, O. and R. W. Gerard. *J. Neurophysiol.* 1: 558, 1938.
274. Sweet, W. H., G. A. Talland and F. R. Ervin. Loss of recent memory following section of the fornix. *Tr. Am. Neurol. A.* 76, 1959.
275. Symposium: Conditioning of the EEG in animal and man. American Electroencephalographic Society, 13th Annual Meeting, 1959.
276. Tauc, L. Evidence of synaptic inhibitory actions not conveyed by inhibitory post-synaptic potentials. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
277. Terzuolo, C. A., B. Sigg and K. F. Killam. Discussion. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
278. Thompson, R. *Psychol. Rep.* 3: 183, 1957.
279. Thompson, R. and D. F. Pennington. *J. Comp. & Physiol. Psychol.* 50: 401, 1957.
280. Tobias, J. M. *J. Cell. & Comp. Physiol.* 52: 89, 1958.
281. Tobias, J. M. *Ann. Rev. Physiol.* 21: 299, 1959.
282. van Breeman, V. L., E. Anderson and J. F. Reger. *Exper. Cell Res.* Suppl. 5: 153, 1958.
283. van Harreveld, A. and S. Ochs. *Am. J. Physiol.* 189: 159, 1957.
284. Vickers, G. The concept of stress in relation to the disorganization of behavior. In: *Stress and Psychiatric Disorder*, edited by J. M. Tanner. Oxford: Blackwell. In press.
285. von Békésy, G. *J. Acoust. Soc. Am.* 31: 338, 1959.
286. von Foerster, H. Quantum theory of memory. In: *Cybernetics*, edited by H. von Foerster. New York: Macy, 1950, p. 112.
287. von Neumann, J. *The Computer and the Brain*. New Haven: Yale Univ. Press, 1958.
288. Waelsch, H (editor). *Biochemistry of the Developing Nervous System*. New York: Acad. Press, 1955.
289. Waller, A. D. *Phil. Trans. B* 188: 1, 1897.
290. Walter, W. G. *The Living Brain*. New York: Norton, 1953.
291. Weiss, P. Nervous system (neurogenesis). In: *Analysis of Development*, edited by B. H. Willier, P. Weiss and V. Hamburger. Philadelphia: Saunders, 1955, p. 346.
292. Wertheimer, M. and C. M. Leventhal. *J. Exper. Psychol.* 55: 255, 1958.
293. Wiersma, C. A. G. Introductory remarks, Second Session. In: *Inhibition in the Nervous System and Gamma-aminobutyric Acid*, edited by E. Roberts. New York: Pergamon Press. In press.
294. Williams, C. M. *Harvey Lectures* 47: 126, 1953.
295. Williams, D. *J. Neurol. & Psychiat.* 4: 257, 1941.
296. Windle, W. F. (editor). *Regeneration in the Central Nervous System*. Springfield: Thomas, 1955.
297. Wynne, L. C. and R. L. Solomon. *Genet. Psychol. Monogr.* 52: 241, 1955.
298. Wyss, O. A. M. *Helvet. physiol. et pharmacol. acta* 12, Suppl. 10: 5, 1954.

AUTHOR AND SUBJECT INDEXES
VOLUMES I-III

# Author index, volumes I-III

*Volume I: pages 1–780  Volume II: pages 781–1440  Volume III: pages 1441–1966*

# Subject index, volumes I-III

*Volume I: pages 1–780* *Volume II: pages 781–1440* *Volume III: pages 1441–1966*